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Summary Review of the Health Effects Associated with Copper: Health Issue Assessment

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16. ABSTRACT

This Health Assessment Summary Document is a brief review of the scientific knowledge on copper. The emphasis of the document is on inhalation exposure from atmospheric copper and the environmental, ecological and health effects from the species of copper expected to be present in the atmosphere. The document is the scientific supporting basis for EPA decision-making concerning regulation of copper under the Clean Air Act.

Specific scientific documentation on copper under the following headings is found in the document: Physical and Chemical Properties, Analytical Methods, Fate and Transport, Environmental and Exposure Levels, Pharmacokinetics, Toxicology and Human Health Effects.

Ambient air exposure to copper adds little to the copper body burden for normal individuals. Human homeostatic mechanisms act to control copper balance in the body. Deficiencies or excesses of copper intake in humans rarely result in copper toxicosis. Special groups of risk include Wilson's disease individuals, children and some populations residing near production and processing facilities.

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Health Issue Assessment

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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Preface

This Health Assessment Summary Document is a brief review of the scientific knowledge on copper. The emphasis of this summary document is on inhalation exposure from atmospheric copper and the environmental, ecological and health effects from the species of copper expected to be present in the atmosphere. Environmental media other than air and occupational exposure is discussed only if a process in that medium has a direct or indirect impact on the atmosphere or if a process in the atmosphere has an impact on other media. The information provided in this summary document indicates areas where adequate data are available and areas where the data are limited or lacking. Information on copper summarized in this document has been obtained from examination of primary scientific literature identified through a computerized literature search, a subsequent peer-review workshop and major literature published since that workshop in 1985. This selective presentation of the data is designed to illustrate the major environmental and health effects of copper arising from the atmospheric medium.

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List of Abbreviations

AA	Atomic absorption
AE	Atomic emission
BCF	Bioconcentration factor
bw	Body weight
GI	Gastrointestinal
G6PD	Glucose-6-phosphate dehydrogenase
GSH	Glutathione
ICP-AES	Inductively coupled plasma-atomic emission spectroscopy
INAA	Instrumental neutron activation analysis
LD_{50}	Dose lethal to 50% of recipients
MMD	Mass median diameter
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
PVC	Polyvinyl chloride
SGOT	Serum glutamic oxaloacetic transaminase
SRM	Standard reference material
XRF	X-ray fluorescence

Document Development

David J. Reisman, Document Manager
W. Bruce Peirano, Document Manager
Environmental Criteria and Assessment Office, Cincinnati
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency

Jerry F. Stara, Director
Environmental Criteria and Assessment Office, Cincinnati
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency

Authors and Major Contributors:

David J. Reisman
W. Bruce Peirano
Environmental Criteria and Assessment Office, Cincinnati
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency

Jonathan B. Lewis
Dipak K. Basu
David Hohrseiter
Michael Neal
Syracuse Research Corporation
Syracuse, New York

Scientific Reviewers and Contributors:

Harlal Choudhury
Environmental Criteria and Assessment Office, Cincinnati
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency

Beth Hassett, OAQPS Project Manager
John J. Vandenberg
Office of Air Quality Planning and Standards
Research Triangle Park, NC

Richard Walentowicz
Exposure Assessment Group
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Robert Beliles
Carcinogen Assessment Group
Office and Health and Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Lawrence Valcovic
Reproductive Effects Assessment Group
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

External Consultants:

Thomas Clarkson
Division of Toxicology
University of Rochester School of Medicine
Rochester, NY

Joan Cranmer
Department of Pediatrics #512B
University of Arkansas for Medical Sciences
Little Rock, AR

Vincent N. Finelli
Toxicology Consultant
497 N.W. 15th Street
Boca Raton, FL

Rolf Hartung
Professor of Environmental Technology
University of Michigan
Ann Arbor, MI

Paul Mushak
Department of Pathology
University of North Carolina
Chapel Hill, NC

Herbert E. Stokinger
Toxicology Consultant
9 Twin Hills Ridge Drive
Cincinnati, OH

Editorial Reviewer:

Judith Olsen
Environmental Criteria and Assessment Office, Cincinnati
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency

Document Preparation:

Patricia A. Daunt
Bette L. Zwayer
Environmental Criteria and Assessment Office, Cincinnati
Office of Health and Environmetal Assessment
U.S. Environmental Protection Agency

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Summary

Copper is a metallic element belonging to group IB of the periodic table. The United States production of copper in 1981 was 1.54 million metric tons, compared to a demand of 2.35 million metric tons. Most copper compounds occur in +1 and +2 valence states. The Cu(I) ion is unstable in aqueous solution; however, Cu(I) can be stabilized in aqueous solution by some ligands. The Cu(II) species, on the other hand, is stable in aqueous solution. Although copper is present as numerous chemical species, the biological availability and toxicity of copper is probably related to free Cu^{2+} ion activity.

A large number of methods are available for the analysis of copper in different matrices. In ambient air, copper is commonly sampled with high volume samplers. Isokinetic sampling has been used for the collection of copper from industrial plumes. The most widely used methods for the determination of copper are atomic absorption, atomic emission, X-ray fluorescence and neutron activation analysis. The precision and accuracy of a method for the quantification of copper depends both on the method used and the sample matrix under analysis. The detection limits of copper in water solution with the four most widely used methods are in the ppb or sub-ppb range. The precision of copper analysis is usually lower as the complexity of the sample matrix increases (e.g., the precision of copper analysis is higher for particulate copper collected from an industrial area than in the case of copper in biological samples).

On a global basis, the atmospheric copper flux from anthropogenic sources are ~3 times higher than its flux from natural sources. Non-ferrous metal production is the largest contributor of atomspheric copper flux in the United States. It has been estimated that the atmospheric emission rate of copper from anthropogenic sources in the United States in the 1980's ranges from 940×10^3 kg/year to 8200×10^3 kg/year. Atmospheric deposition plays a major role in the overall copper loading to both surface water and soil. The majority of copper produced in the United States is used as the metal and its alloys and <5% is used for the production of chemical compounds. By far, the highest utilized copper compound in the United States is copper sulfate.

A few studies on the fate and transport of copper in the atmosphere are available, but some data gaps still exist. The average MMD for copper aerosols in the United States is 1.3 μm. Since particulate matter in the size range of 0.5 and 5.0 μm is commonly assumed to be respirable, the copper particles in United States aerosols predominantly occur in the respirable range. The chemical form of copper in aerosol is not well studied. It has been speculated that copper sulfides, oxides and sulfate and possibly silicate may originate from mining and ore crushing and beneficiation processes. Smelting operations may produce oxides, sulfate and elemental copper. Although no direct experimental evidence exists, it is likely that municipal incineration will produce copper and copper oxide in its emission.

It has also been speculated that copper sulfate may also be formed in the atmosphere through the reaction of copper oxide with sulfur dioxide in the presence of oxygen. There is some experimental evidence that elemental copper, copper oxide and $CuFeS_2$ are present in the atmosphere near smelting areas. The primary modes of copper removal from the

atmosphere are dry deposition (dustfall) and wet deposition (rainfall and snowfall). The copper content of dustfall varies from 20 to >50,000 μg/g near smelters. Although the ratio of wet to dry deposition is dependent on several factors, the typical ratio is close to unity. There is some evidence of long range transport of copper from polluted areas. It has been speculated that the atmospheric residence time of copper in the unpolluted troposphere is 2-10 days. In urban and polluted areas, the residence time may be even shorter. It is unlikely for copper to reach the stratosphere at levels that could cause a significant reaction or any depletion of the ozone layer.

The average atmospheric level of copper in the 1970's was 0.4 ng/m^3 in remote areas, 25 ng/m^3 in rural areas, 160 ng/m^3 in urban areas and 190 ng/m^3 in suburban areas. Although the introduction of clean air regulations in the United States have resulted in ~20% reduction in airborne particulates from 1970-1974, the atmospheric copper levels in the United States have not changed and may have remained constant between 1965 and 1974. Limited data presented in this document,however, indicate that a decrease in atmospheric copper concentration may be taking place during this decade.

Based on the average atmospheric copper concentration in the United States in the 1970's, the inhalation exposure of copper has been estimated at 0.5 μg/day in rural areas, 3.2 μg/day in urban areas and 3.8 μg/day in suburban areas. The average daily intake of copper through drinking water in the United States is 260 μg/day and <2000-4000 μg/day through foods. Several reviews of copper toxicity have indicated that the contribution of atmospheric copper to the total daily intake and body burden is very minor. Therefore, the daily intake of copper through inhalation is negligible compared to its intake through ingestion. The mechanisms surrounding any toxicity of copper are different depending on the route of exposure.

Copper is an element essential for proper nutrition and is distributed throughout the body. Absorption of copper and copper compounds can occur by oral and inhalation routes of exposure, with highest uptake rates occurring in the GI tract followed by respiratory absorption. Very little percutaneous absorption occurs. Copper can also cross the placental barrier and is taken up by the fetus. Only 20% of inhaled copper mists, fumes or dusts is estimated to be absorbed by the lungs, with the remainder removed by the bronchial mucosa or deposited unabsorbed in the lung tissue. Studies using radioactive copper have demonstrated that 32-70% of ingested copper is absorbed through the GI tract. As discussed in this document, inhaled copper may actually be ingested and absorbed through the GI tract. This occurs when the human homeostatic mechanisms create a "coughing and swallowing" action, leading to ingestion of copper. In the blood, absorbed copper is bound to ceruloplasmin as well as amino acids and albumin, which function as the main distributors of copper in the body. The copper body burden in adults ranges from 70-120 mg with the liver acting as the main storage organ. Other organs containing high copper concentrations include the brain, heart and kidneys. Fetal copper content and distribution differs from that observed in adults in that total body content and liver concentration of copper are much higher in the fetus.

Fecal excretion is the primary route of copper elimination and consists mostly of unabsorbed dietary copper as well as body copper eliminated through biliary clearance and intestinal mucosal secretion. Relatively lesser amounts of copper are also found in urine, sweat, saliva, hair, nails and menstrual fluid.

The pharmacokinetic properties of copper in animals and humans demonstrate that sophisticated homeostatic mechanisms have evolved to cope with copper intake deficiencies and excesses. Despite fluctuations in

copper intake, proper copper balance in the body can be maintained by varying the amount of copper absorbed and excreted and by altering copper's distribution to various tissues. In this way, the nutritional status of the organism is normally matched with daily intake to maintain a physiologically optimal level of copper in the body. It should be noted that since the pharmacokinetic properties of copper were elucidated using predominantly oral exposure, the question of whether these same mechanisms are effective for other routes of exposure (inhalation, dermal, transplacental) still remains.

As a required element, copper is incorporated into >12 specific copper proteins, such as cytochrome oxidase, tyrosinase and erythrocyte superoxidedismutase. Copper is essential for hemoglobin formation, carbohydrate metabolism, catecholamine biosynthesis, and cross-linking of collagen, elastin and hair keratin. Other metals such as zinc, iron and molybdenum interact with copper to affect copper's absorption, distribution, metabolism and utilization.

Because of well-developed homeostatic mechanisms, episodes of toxicosis from excess copper exposure in man and animals are relatively rare. There is a notable lack of information concerning the pharmacokinetics and toxic effects of inhaled copper in experimental animals. Limited inhalation studies with copper compounds generally resulted in minor, transient effects in experimental animals; however, guinea pigs exposed to Bordeaux mixture, a fungicide containing copper sulfate, exhibited various lung lesions. The available data from copper inhalation studies are limited in their usefulness for predicting and assessing human risk, since the issue of systemic toxicity resulting from copper in the atmosphere was not addressed. Most of these studies have mixed exposures or have been done using a copper-related compound or salt.

Acute and subchronic oral toxicity studies have shown that copper can elicit a wide range of toxic effects in the liver, kidneys, blood, GI tract, brain and fetus. The doses used in these studies, however, generally were much higher than those levels likely to be encountered by human consumption. Oral ingestion of large quantities of copper compounds in swine and rats resulted in heavy copper deposition and necrosis in the liver and kidneys, as well as hemolytic anemia and GI irritation. Limited evidence of teratogenicity in mice and hamsters was reported, though the administered doses were very high and the routes of exposure were primarily not relevant to human exposure situation. Equivocal results have been obtained from studies designed to test the mutagenicity and carcinogenicity of copper compounds. Using USEPA Guidelines for Carcinogen Risk Assessment, the overall weight of evidence suggests that there is insufficient data to determine the carcinogenic potential of copper to humans, and therefore, copper is in Group D: Not classifiable.

Occupational exposure to copper mists, fumes and dusts has reportedly caused a transient condition known as "metal fume fever," a disorder characterized by influenza-like symptoms. Vineyard workers exposed to Bordeaux mixture reportedly had various histological lesions in the lungs and liver.

Reports of copper intoxication most often arise from accidental poisonings or suicide attempts using copper sulfate or from the consumption of water containing high copper concentrations. A number of symptoms have been reported from these incidents including gastrointestinal irritation, headache, dizziness, hemolytic anemia, hematuria and reduced glucose-6-phosphate dehydrogenase activity. More serious cases have involved ulceration of the gastric mucosa, hepatic and renal necrosis, coma and death. Indian Childhood Cirrhosis, a condition affecting certain segments of the Indian population, is characterized by widespread hepatic necrosis and extremely high hepatic

copper levels. This disease is throught to arise, in part, from the leaching of copper into milk and water stores, leading to excess copper intake in children. Epidemiology studies have reported marginal evidence linking copper smelters and excess dietary copper to increased incidences of cancer, mortality and central nervous system congenital malformations. These data, however, are confounded by the presence of other metals such as arsenic leading to uncertainty in the interpretation of the results.

The population most sensitive to elevated environmental copper levels is that afflicted with Wilson's disease (~1 in 200,000 individuals). These individuals represent a documented case of endogenous chronic copper toxicosis in man. Hepatic ceruloplasmin synthesis is severely impaired and copper levels in all tissues, especially in liver, are markedly increased, thus causing these people to be extremely vulnerable to minor variations in copper intake. Reports of Indian Childhood Cirrhosis and copper intoxication in children exposed to food and water contaminated with higher copper levels represent external exposure situations, and indicate that newborns and young children are more sensitive to excess copper than are normal adults. Increased copper concentrations in the body and underdeveloped homeostatic mechanisms probably contribute to this susceptibility. One study indicates that 13% of the Black American male population has red cell G6PD deficiency which could be at an increased risk to environmental oxidants. Another study disagrees with this issue and is reviewed in this document.

In summary, human homeostatic mechanisms act to control copper balance by regulating the absorption, storage, distribution, utilization and excretion of the metal. Deficiencies or excesses in copper intake rarely result in episodes of copper toxicosis. In cases where homeostatic mechanisms are genetically disrupted as in Wilson's disease or underdeveloped as in the fetus and young children, excess copper intake is not regulated resulting in the symptoms of copper toxicosis. Very few cases of intoxication from airborne copper in the workplace have been reported, indicating that acute occupational exposure to copper dusts or fumes has not been a significant toxic health hazard. The role which homeostatic mechanisms play in controlling the pharmacokinetics of inhaled copper has yet to be investigated.

Atmospheric inputs of copper and other compounds and metals have been found to cause adverse effects in terrestrial and aquatic ecosystems. These effects range from complete destruction of terrestrial vegetation in areas immediately downwind from copper smelters to more subtle ecological effects such as disruption of nutrient cycling or elimination of sensitive species and potential disruption of food chains. Accumulation of copper in terrestrial plants can also lead to toxic effects in herbivore populations such as sheep, which are sensitive to copper poisoning. The available information indicates, however, that atmospheric copper inputs in most areas of the United States are generally not large enough to cause significant ecological effects in terrestrial and aquatic ecosystems. Effects may occur, however, in certain "hot spots" receiving unusually high copper inputs.

2. Physical and Chemical Properties

Copper is a metallic element that is listed as the first element of subgroup IB of the periodic table. Although copper occurs naturally as the free metal, 80% of the copper production is refined from low grade minerals containing ≤2% of the metal. A few of the common copper-containing ores used to derive the metal are: chalcocite, Cu_2S; covellite, CuS; chalcopyrite, $CuFeS_2$; cuprite, Cu_2O; tenorite, CuO; and malachite $Cu_2CO_3(OH)_2$ (Stokinger, 1981; Demayo et al., 1982).

Although copper and its compounds occur in four oxidation states, the 0, +1 and +2 valency states are the most common. The consumption of a few selected copper compounds in the United States in 1975 was as follows (Kust, 1979):

copper (II) sulfate:	35,600 tons
copper (II) naphthenate:	450 tons
copper (I) oxide:	200 tons
copper (II) oleate:	100 tons
copper (II) carbonate:	50 tons

The United States production of Cu(I) oxide in 1981 was 4661 tons (U.S. Dept. of Commerce, 1983) and 4616 tons in 1976 (U.S. Dept. of Commerce, 1982). Considering the United States consumption and production data, it can be concluded that Cu(I) oxide is largely exported. The relevant physical properties of these copper compounds and a few other commonly used copper compounds [Cu(II) acetate, Cu(I) chloride, Cu(II) chloride, Cu(II) nitrate, Cu(II) oxide] are given in Table 1. Cu(II) arsenate, Cu(I) cyanide and Cu(II) phthalocyanides are also produced in high volume in the United States (SRC, 1980). These compounds have been excluded from the table, however, because their observed health effects may be attributed to the anionic portion of the compounds and should be included in a discussion of cyanide and arsenic compounds, not copper.

The relative stabilities of Cu(I) and Cu(II) states are indicated by the following reduction potential data (Kust, 1979):

$Cu^{+} + e \rightarrow Cu$	$E^{\circ} = 0.521V$
$Cu^{2+} + e \rightarrow Cu^{+}$	$E^{\circ} = 0.153V$
$Cu^{2+} + 2e \rightarrow Cu$	$E^{\circ} = 0.337V$

Therefore, any system with the oxidation potential of >0.153V will oxidize Cu^{+} ions to Cu^{+2} ions. The Cu(I) ion is unstable in aqueous solution; consequently, only small concentrations of Cu^{+1} can exist in aqueous solution. In the presence of some ligands, however, Cu(I) can be stabilized in aqueous solution (Kust, 1979). The Cu(II) species is stable in aqueous solution. In most natural waters containing carbonates, Cu^{+2} ions exist up to pH 6 and $CuCO_3$ exists in the pH range 6-9.3 (Stumm and Morgan, 1970). Although copper is present as numerous chemical species in aquatic media, the *in situ* biological availability and toxicity of copper is probably related to free Cu^{+2} ion activity (Sanders et al., 1983).

Copper forms complexes with several inorganic and organic compounds and the stability of such complexes is dependent upon the pH, temperature

Table 1. Selected Physical Properties of Copper and Some Copper Compounds[a]

Chemical	Formula	CAS Registry No.	Atomic or Molecular Weight	Appearance	Density or Specific Gravity	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure	Aqueous Solubility
Copper	Cu	7440-50-8	63.55	reddish metal	8.92	1083.4	2567	1 mm Hg at 1628°C	insoluble
Copper (II) acetate, monohydrate	$Cu(C_2H_3O_2)_2 \cdot H_2$	142-71-2	199.65	dark green powder	1.882	115	decomposes at 240	NA	72 g/l in cold water[b]
Copper(II) carbonate, basic	$CuCO_3Cu(OH)_2$	12069-69-1	221.11	dark green crystal	4.0	decomposes at 200°	NR	NA	insoluble in cold water but decomposes in hot water
Copper (I) chloride	CuCl (or Cu_2Cl_2)	7758-89-6	98.99	white crystal	4.14	430	1490	1 mm Hg at 546°C	0.062 g/l in cold water
Copper(II) chloride	$CuCl_2$	7447-39-4	134.44	brown or yellow hygroscopic powder	3.386^{4}_{25}	620	decomposes at 993	NA	706 g/l at 0°C
Copper (II) naphthenate	Cu-salt of naphthenic acid also called cuprinol	1338-02-9	variable	green-blue solid	NA	NA	NA	NA	NA
Copper (II) nitrate, trihydrate	$CuNO_3 \cdot 3H_2O$	10031-43-3	241.60	blue deliquescent crystal	2.32^{4}_{25}	114.5	decomposes at 170	NA	1378 g/l at 0°C

Table 1. (continued)

Chemical	Formula	CAS Registry No.	Atomic or Molecular Weight	Appearance	Density or Specific Gravity	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure	Aqueous Solubility
Copper(II) oleate	$Cu(C_{18}H_{33}O_2)_2$	1120-44-1	626.47	brown powder or green-blue solid	NA	NA	NA	NA	insoluble
Copper(I) oxide	Cu_2O	1317-39-1	143.08	reddish, crystal	6.0	1235	decomposes at 1800°C	NA	insoluble
Copper(II) oxide	CuO	1317-38-0	79.54	black crystal	6.3-6.49	1326	NA	NA	insoluble
Copper(II) sulfate, pentahydrate	$CuSO_4 \cdot 5H_2O$	7758-99-8	249.68	blue crystal	2.284	decomposes at 10°C	NR	NA	316 g/l at 0°C

[a] Source: Weast, 1980; SRC, 1980.
[b] The temperature of cold water was not specified.
NA = Not available; NR = Not relevant.

and concentration of the ligands (Cotton and Wilkinson, 1980; USEPA, 1980b). In the atmosphere, the following chemical reactions of copper oxides have been speculated to occur (Nriagu, 1979):

$$CuO + SO_2 + O_2 \sim CuSO_4 \rightarrow$$

$$2\ Cu_2O + 2SO_2 + 2O_2 + 2H_2O\ (\text{vapors}) \rightarrow Cu^3(OH)SO_4 + CuSO_4$$

The details of other chemical reactions of copper are reported in Cotton and Wilkinson (1980). Very little is known about the possible heterogenous reactions of copper (reactions of particulate copper with gaseous compounds in the atmosphere) and its compounds in the atmosphere. Metallic copper may oxidize in air with the formation of hydroxo carbonate $Cu_2(OH)_2CO^3$ (Cotton and Wilkinson, 1980). Whether the oxides of copper can form copper nitrate as a result of reactions with oxygen and oxides of nitrogen under atmospheric conditions is not known.

3. Sampling and Analytical Methods

A large number of publications are available that deal with the sampling and analysis of copper in different matrices. References to a few publications in the subsequent discussion does not necessarily mean that these are the only key publications on the subject. These publications have been used to illustrate the different methods available for the sampling and analysis of copper.

The sampling of copper in ambient and occupational air is usually performed by collecting airborne particulate copper on glass fiber, PVC or cellulose acetate filters (Wilson et al., 1981; Moyers et al., 1977; Hammerle et al., 1973; NIOSH, 1978). High volume samplers and a longer sampling time are used for the collection of samples where the copper concentration is low, as in the case of ambient air. The selection of a filtering medium is important since the impurities in the filters may contribute to a high background reading. For the separation of airborne particulate matter into different size fractions, cascade impactors are used (Paciga and Jervis, 1976; Chan et al., 1983; Lee et al., 1972). The isokinetic sampling of copper from industrial plumes has also been described (Small et al., 1981; Serth and Hughes, 1980; Que Hee et al., 1982), and is usually done with a modified USEPA method 5 sampling train (Que Hee et al., 1982; Serth and Hughes, 1980).

The sampling of copper from aquatic, biological, soil and sediment media is normally performed by the grab method, although proportional samplings with mechanical samplers can be used for composite sampling of industrial wastewater samples (Sandhu et al., 1977; Hogan and Wotton, 1984; Strain et al., 1975; Young and Blevins, 1981; Wood and Nash, 1976; Lytle and Lytle, 1982). For collection of sediment samples from different depths, gravity cores have been used (Stoffers et al., 1977).

Several methods are available for the analysis of copper. One of these methods is direct aspiration atomic absorption with and without complexation of copper (Lytle and Lytle, 1982; NIOSH, 1978; Chambers and McClellan, 1976). The complexation method increases the sensitivity by orders of magnitude over direct aspiration (Chambers and McClellan, 1976) as a result of concentration of the Cu-complex from the aquatic to organic phase and the enhancement of the atomic absorption signal due to the solvent. The atomic absorption technique with a graphite furnace has higher sensitivity than the direct aspiration atomic absorption method (Strain et al., 1975; Koizumi et al., 1977; Geladi and Adams, 1978; Young and Blevens, 1981). In the graphite furnace method, the sample can be introduced directly into the graphite tube without further treatment. To minimize matrix interference a deuterium arc or xenon arc background corrector is normally used with graphite furnace atomic absorption. A graphite furnace atomic absorption background corrector based on the polarization characteristics of the Zeeman effect was developed by Koizumi et al. (1977). This method was claimed to reduce matrix interference to such an extent that no sample ashing was required for the quantification of low level copper in serum and urine samples. The probability of copper loss through volatilization during the ashing process (a process used to reduce matrix interference), however, is minimal as long as the ashing temperature does not exceed 800°C (Geladi and Adams, 1978). Additional information on this subject is reported by Van Ormer (1975).

Inductively coupled plasma-atomic emission spectroscopy has also been used for the analysis of copper (Que Hee et al., 1982; Aziz et al., 1982; Boorn and Browner, 1982). With a concentric nebulizer, the sensitivity of copper determination increased in many organic solvents (e.g., xylenes, butanol), but no increase was observed with a crossflow nebulizer (Boorn and Browner, 1982). The X-ray fluorescence method has been used by several investigators (Giaque et al., 1977; Van Grieken, 1977; Ragaini et al., 1977); however, errors may occur due to the matrix effect with such samples as soil. This problem has been overcome by fusion of the samples with lithium metaborate or sulfur powder (Giaque et al., 1977; Ragaini et al., 1977). The neutron activation analysis has also been used for the quantification of copper (Dams et al., 1970; Ragaini et al., 1977; Small et al., 1981). While direct gamma counting with a Ge(Li) detector following neutron irradiation by instrumental neutron activation analysis was successful for the quantification of copper in air pollution particulates, this method was not suitable for biological samples. Guzzi et al. (1976) demonstrated that an extensive radiochemical group separation procedure was necessary before counting gamma activity for biological samples containing low levels of copper.

Copper has been analyzed by the following methods that are not commonly used: kinetics of a catalytic reaction (Igov et al., 1980); X-ray photoelectron spectroscopy (Holm and Storp, 1976); anode stripping voltametry (Lund and Onshus, 1976; Woolston et al., 1982); gas chromatography with flame ionization detection (Uden and Waldman, 1975); ring oven technique (West and Sachdev, 1969); thin-layer chromatography (Bark et al., 1971); spectropolarimetric (Mirti, 1974); colorimetric (NAS, 1977); spectrofluorimetric (Lazaro Boza et al., 1984); chemiluminescence (Wehry and Varnes, 1973); ion scattering spectrometry; and secondary ion mass spectrometry (Karasek et al., 1978).

The most widely used methods for the determination of copper are atomic absorption, atomic emission, X-ray fluorescence and neutron activation analysis. The analysis of copper in air particulates by atomic absorption and atomic emission is commonly done by wet digestion of the filter paper with nitric acid/hydrochloric acid, or a nitric acid/perchloric acid mixture in open beakers. An additional hydrofluoric acid digestion step is used for airborne particulate samples that may contain copper associated with silica either as silicate or sorbed on silica, as in the case of fly ash from power plants (Que Hee et al., 1982; Moyers et al., 1977). Since the hydrofluoric acid digestion step may cause loss of some elements due to volatilization (e.g., B and Si), digestion in Parr acid digestion bombs has also been used (Moyers et al., 1977). Digestion in Parr bombs, however, is not necessary for copper determination. The acid digested aqueous solution at a proper pH is then quantified for copper by atomic absorption in the flame or flameless (graphite furnace) mode, or by inductively coupled plasma-atomic emission spectroscopy. The analysis of copper in air particulate by instrumental neutron activation analysis is done by placing the whole or a part of the filter in a polyethylene bag and irradiating it with a neutron source. The quantification is done by counting the γ-radiation with Ge(Li) detectors (Dams et al., 1970; Small et al., 1981; Ragaini et al., 1977). In X-ray fluorescence analysis of copper in air particulate matter, discs cut from filter paper are mounted on the instrument and the Kα X-rays are used for the quantification (Hammerle et al., 1973; Ragaini et al., 1977).

The analysis of copper in blood and urine or tissue is usually performed by wet ashing with a sulfuric/perchloric acid mixture (NAS, 1977) and by quantifying with the atomic absorption method. A graphite furnace atomic absorption with a background corrector based on the Zeeman effect, however, has been used for the direct quantification of copper in serum and urine

samples without the prior ashing step (Koizumi et al., 1977). The analysis of biological samples containing low levels of copper by neutron activation analysis will require an extensive radiochemical group separation procedure to eliminate interference during the gamma-counting step of the quantification procedure (Guzzi et al., 1976). A procedure where the lyophilized dry muscle of aquatic organisms are pulverized and pressed into pellets for the determination of copper by X-ray fluorescence has been described by Popham and D'Auria (1983).

The precision and accuracy of a certain method for the quantification of copper depends not only on the method used, but also on the sample matrix. Ideally, this precision and accuracy can be best evaluated by analyzing standard reference materials containing copper in the same matrix as the sample that is being analyzed. A few such standard reference materials for copper are available from the National Bureau of Standards which provides standard bovine livers (Lytle and Lytle, 1982); coal standards, SRM 1632a and 1635 (Small et al., 1981); orchard leaves, SRM 1571 (Woolston et al., 1982); fly ash standard, SRM 1633 (Ragaini et al., 1977) containing known amount of copper. The International Atomic Energy Agency provides several biological samples with certified copper values (Lytle and Lytle, 1982). The USEPA and U.S. Geological Survey may be a source of water standards (Strain et al., 1975). The detection limits and the advantages and disadvantages of copper quantification by the widely used methods are given in Table 2.

Table 2. The Detection Limits, Advantages and Disadvantages of Selected Methods for the Determination of Copper

Method	Detection* Limit	Advantages and Disadvantages	Reference
AA—direct aspiration	2 ppb	The method is simple and instrumentation is available in most labs. Method is destructive and will not allow simultaneous determination of other metals.	Fernandez and Manning, 1971
AA—flameless	0.1 ppb	Same as AA method, but the method is faster and has lower detection limit, but has less precision than flame AA.	Fernandez and Manning, 1971
ICP—AES	2-3 ppb	The method is rapid and versatile, but is destructive. It will not allow simultaneous determination of other metals.	Que Hee et al., 1982; Boorn and Browner, 1982
AA—complexation	0.01 ppb	The method is the same as AA or AES, but provides lower detection limit. It is more time-consuming.	Chambers and McClellan, 1976; Boorn and Browner, 1982
INAA	0.05 µg	Method is non-destructive and will allow simultaneous determination of many metals. Instrumental facility available to limited laboratories.	Dams et al., 1970
XRF	0.4 ppb	Same as INAA, but the precision and accuracy could be less.	Van Grieken et al., 1977

*Detection limits are for simple aqueous solutions. Complex matrices with high background may have considerable higher detection limits; ppb for solution = µg/l; ppb for solid matrix = µg/kg.

4. Sources and Uses in the Environment

The United States production of copper was 1.45 million metric tons in 1974, 1.46 million metric tons in 1976 and 1.54 million metric tons in 1981. An additional 0.60 million metric tons were produced in 1981 from old scrap. The United States demand for copper in 1981 was 2.35 million metric tons. An estimated 0.76 million metric tons of copper were imported in the United States in 1981. Industry stocks account for the rest of the U.S. copper supply in 1981 (Stokinger, 1981; Tuddenham and Dougall, 1979; Weant, 1985). The principal copper-processing states in the United States in 1984 and their percentages of the total were: Arizona, 73.3%; Montana, 8.4%; New Mexico, 7.7%; Utah, 4.8%; and Michigan, 4.3% (Weant, 1985). The primary copper smelting states in the United States in 1984 with percentages of the total were: Arizona, 63.9%; Utah, 12.5%; Michigan, 10.5%; Nevada, 6.2%; and New Mexico, 3.7% (Weant, 1985).

The sources of copper in the environment are reasonably well-studied. Both anthropogenic and natural sources contribute to the emission of copper to the atmosphere. Table 3 lists the worldwide copper emission sources in the atmosphere in 1975, showing that windblown dust accounts for ~65% of the overall nonanthropogenic sources of copper emission to the atmosphere. Nonferrous metal production, wood combustion, and iron and steel production constitute ~69% of the overall emission from anthropogenic sources. It can be concluded from Table 3 that the atmospheric copper flux from anthropogenic sources are ~3 times higher than its flux from natural

Table 3. Sources of Worldwide Copper Emission to the Atmosphere in 1975*

Source	Emission Rate (10^3 MT/year)
Natural:	
windblown dust	*12*
volcanoes	*3.6*
vegetation	*2.5*
forest fires	*0.3*
sea spray	*0.08*
Total	*18.5*
Anthropogenic:	
nonferrous metal production	*21.2*
wood combustion	*11.5*
iron and steel production	*6.3*
coal combustion	*5.6*
waste incineration	*5.3*
industrial applications	*4.9*
nonferrous metal mining	*0.8*
oil and gasoline combustion	*0.7*
Total	*56.3*

**Source: Nriagu, 1979*
MT = Metric ton

sources. Global anthropogenic emissions of copper have been increased from 23,000 metric tons during the period 1951-1960, to 43,500 metric tons during the period 1961-1970, to 58,500 metric tons during 1971-1980 (Davies and Bennett, 1983). The anthropogenic atmospheric emission sources of copper in the United States in 1984 are shown in Table 4. It can be concluded from Table 4 that ore processing and smelting are the primary sources of anthropogenic copper in the United States atmosphere constituting 77.8% of the overall anthropogenic input. Other sources of copper emission are: iron and steel production, 7.4%; coal and oil combustion, 4.6%; zinc smelting, 3.3%; copper sulfate production, 2.7%; municipal incineration, 1.9%; others, 2.3% (Weant, 1985). A comparison of Tables 3 and 4 indicates that a maximum of 14.6% of the worldwide copper emission to the atmosphere originates from the United States. Considering that the U.S. copper production in 1975 constituted ~18.4% of the world production (Tuddenham and Dougall, 1979), the overall atmospheric emission estimate given in Table 4 is likely to be a conservative estimate.

Table 4. Atmospheric Copper Emission Sources in the United States in 1984*

Source	*Emission Rate (MT/year)*
Ore processing	*480-660*
Ore smelting	*203-6160*
Iron and steel production	*112-240*
Coal and oil combustion	*45-360*
Copper sulfate production	*45*
Zinc smelting	*24-340*
Carbon black production	*13*
Iron foundries	*7.9*
Lead smelting	*5.5-65*
Municipal incineration	*3.3-270*
Ferro alloy production	*1.9-3.2*
Brass and bronze production	*1.8-36*
Total	*942.4-8200.1*

**Source: Weant, 1985*
MT = Metric ton

Although the overall amount of atmospheric emissions of copper in the United States are from the sources given in Table 4, the contribution of different sources in any given area is strongly dependent upon the localized conditions. For example, it was estimated that 81 and 12% of the copper aerosol in New York City was from incineration and automobile emission, respectively, and 37, 31, 22% and 10% of the copper aerosol in Cleveland, OH, was from incineration, coal combustion, gasoline combustion and distillate fuel combustion, respectively (Nriagu, 1979).

The sources of copper in surface water in the United Kingdom was estimated by Critchley (1983). Atmospheric deposition, river discharge, direct discharges to coastal waters and estuaries, industrial waste and sewage sludge dumping contributed 57, 33, 5, 3 and 2%, respectively, of the total copper input to the North Sea. A similar loading pattern was also estimated for Lake Michigan, where atmospheric deposition, stream discharge and shoreline erosions constituted 56.7-79.4%, 25.1-37.6% and 5.5-5.7%, respectively of the total copper loading (Schmidt and Andren, 1984). Critchley (1983) studied the sources of copper in agricultural land in the United Kingdom and estimated

that atmospheric deposition, sewage sludge, inorganic phosphatic fertilizers and miscellaneous other sources contributed to 77, 6, 1 and 16% of the overall loading of copper. It can be concluded from the above discussions that atmospheric deposition plays an important role in the overall copper loading to both large bodies of surface water and soil. In small water bodies, however, localized sources may overshadow input from atmospheric deposition, especially in rivers in industrialized areas. Examples of the localized sources include effluents from industrial operations, storm water runoff from city streets or agricultural lands, and water from mine drainage (Demayo et al., 1982).

The majority of copper produced in the United States in 1976 was used as the metal and its alloys, and only 5% was devoted to other uses including the manufacture of copper chemicals. In 1976, the following categories accounted for the overall usage of copper in the United States: electrical equipment and supplies, 53.8%; construction materials, 15.4%; transportation industry and machinery, 10.7%; ordinance materials, 1.6%; and other uses (including chemical production and coin making), 5% (Tuddenham and Dougall, 1979, Weant, 1985).

Some of the uses of copper compounds are in agricultural products (insecticides, fungicides, herbicides), anti-fouling paints, catalysts, corrosion inhibitors, electrolysis and electroplating processes, electronics, fabric and textiles, flameproofing, fuel additives, glass and ceramics. Copper is also used in cement, food and drugs, metallurgy, nylon, paper products, pigment and dyes, pollution control catalyst, printing and photocopying, pyrotechnics and wood preservatives (Kust, 1979).

5. Environmental Fate and Transport

There are a few studies available regarding the fate and transport of copper in the atmosphere. The particle size distribution of copper aerosols is important both in terms of the persistence of the particles in the atmosphere and respirability of the particles. Representative particle-size measurements expressed as mass median diameter (MMD) for copper aerosols in a few United States cities are given in Table 5.

Milford and Davidson (1985) calculated the average MMD for copper to be 1.29 μm. The average MMD of copper aerosol calculated from Table 5 is 1.3 μm. Since particulate matter in the size range of 0.5 μm and 5.0 μm is commonly assumed to be respirable (Nriagu, 1979), the copper particles in United States aerosols predominantly occur in the respirable range. For copper particles of ~1 μm MMD, ~50-60% of the inhaled amount would be expected to be deposited in the pulmonary compartment, ~20-30% in the nasopharyngeal compartment and <10% in the tracheobronchial compartment. About 50-80% of the particles of <1 μm MMD retained in the respiratory system are absorbed into the bloodstream (Nriagu, 1979). It should be recognized, however, that the sizes of copper particles emitted into the atmosphere are source dependent and the MMD data may range from <0.4-10 μm (Nriagu, 1979). It is probable that high temperature processes that volatilize copper also cause the eventual condensation of copper to provide particles of fine particle sizes (Sugimae, 1984). In contrast, copper particles entering the atmosphere through ore crushing and windblown dusts are likely to have a larger particle size. Thus, at least 40% of the total copper particles emitted from non-emission controlled open-hearth furnaces, smelting operations, municipal incineration, and coal combustion produce particles of <2 μm diameter. (Nriagu, 1979). Although direct investigation demonstrating the particle size of copper in windblown dust is not available, the study by Dorn et al. (1976) can be interpreted to conclude that these particles will have larger sizes than particles from high temperature

Table 5. Representative MMD of Copper Particles in Aerosols from Some United States Cities

City, State or Region	MMD (μm)	Reference
Denver, CO	1.54	Lee et al., 1972
Chicago, IL	1.53	Lee et al., 1972
Cincinnati, OH	1.34	Lee et al., 1972
Washington, DC	1.24	Lee et al., 1972
Philadelphia, PA	1.21	Lee et al., 1972
St. Louis, MO	1.07	Lee et al., 1972
San Francisco Bay, CA	3.0	Rahn, 1976
Niles, MI	1.0	Rahn, 1976
Northwest Indiana	0.9	Rahn, 1976
Boston, MA	0.8	Rahn, 1976
Buffalo, NY	0.4	Rahn, 1976
Average (11 locations)	1.8	

MMD = Mass median diameter

processes. Dorn et al. (1976) measured the particle size of copper near a lead smelter and in a remote area (control area) and found that the smelter area contained ~54% of the copper aerosol with a particle size of ≤4.7 μm diameter and the control area, presumably with a higher proportion of windblown dust, contained ~47% of the copper aerosol of diameter ≤4.7 μm.

The chemical form of copper in aerosols has not been well studied. It has been speculated by Nriagu (1979) that copper sulfides, copper oxides, copper sulfates and possibly copper silicate particles may originate from mining, ore crushing and ore beneficiation processes. Smelting operations may produce particles of copper oxides, elemental copper and copper sulfates. Copper brazing from various residential and commercial objects are subjected to municipal incineration and are, therefore, likely to produce emissions containing copper and copper oxide (Jacko and Neuendorf, 1977). Copper sulfate ($CuSO_4$) may also be formed in the atmosphere (O_2) through the following atmospheric reaction, since sulfur dioxide (SO_2) is released during many processes including smelting operations:

$$2\ CuO + 2\ SO_2 + O_2 \rightarrow 2\ CuSO_4$$

Although no direct evidence of the presence of $CuSO_4$ in aerosol was reported, indirect evidence such as the presence of a water soluble fraction in the dust fallout and the presence of an average of 49% soluble fraction in bulk precipitation from Ontario (Nriagu, 1979) suggests that $CuSO_4$ is present in the aerosol.

From measurements of particle density of a collected aerosol in metropolitan Osaka, Japan, Sugimae (1984) presented some indirect evidence that the primary chemical composition of the copper particles consists of copper oxide and elemental copper. The chemical composition of dust particles collected near a copper smelter in Poland was studied using an X-ray diffractometer. The authors presented evidence of the presence of $CuFeS_2$ and $CuAl_2$ in the dust fallout near the smelter (Glowiak et al., 1979).

The removal of copper aerosol from the atmosphere through dry deposition (dust fall) and wet deposition (rainfall and snowfall) has been studied by several investigators because of the possible effects of copper loading on a given ecosystem. The copper content of dustfalls varies from background soil levels of 19-30 μg/g to >50,000 μg/g near smelters. The rate of copper deposition through dustfall may range from <0.02 $\mu g/cm_2$·year in remote locations to >20 $\mu g/cm^2$·year in urban areas (lower Manhattan, NY). The average dry deposition rate for 46 sampling sites in the United States was 3.3 $\mu g/cm^2$·year. The dry deposition velocity of copper aerosol may vary from 0.4 cm/sec in rural areas to 9.5 cm/sec in heavily urbanized areas (Nriagu, 1979). The concentrations of copper in snowfall and rainfall from different locations have also been measured. For example, the copper concentration in rainfall and snowfall at Chedron, NB, was measured to be 4.5 and 4.0 μg/l, respectively, (Struempler, 1976). The ratio of wet to dry deposition of atmospheric copper from several locations has been estimated. Depending on the location, the dry deposition may vary from 2-60% of the total (dry and wet) deposition of atmospheric copper. Although the ratio of wet to dry deposition is dependent upon the particle size distribution, topography of the area and meteorological conditions, the typical ratio is close to unity (Nriagu, 1979). For aerosols with lower particulate sizes, however, the wet deposition rate usually exceeds the dry deposition rate (Davidson et al., 1981; Lannefors et al., 1983).

The possibility of long range transport of copper aerosols was studied by Ouellet and Jones (1983). These authors could not find evidence of any

significant long-range transport of copper into a remote Canadian region from suspected industrial sources. However, the enhancement of copper deposition from the atmosphere into sediments of a remote Adirondack lake in New York, in lake sediments of a remote area in New Hampshire (Galloway and Likens, 1979), and the increase of copper concentration in snowfall and ice-sheets in Greenland with the increase of industrialization (Weiss et al., 1975) show that long-range atmospheric transport of copper is possible.

No direct study estimating the atmospheric residence time of copper aerosols is available; however, it has been estimated that the residence time of copper aerosols in an unpolluted troposphere is 2-10 days, in urban and polluted areas is 0.1 to >4 days, and near an industrial point source (<100 km from source) is <2.0 hours (Nriagu, 1979). Assuming a tropospheric residence time of 10 days and 30 years as the tropospheric to stratospheric turnover time (time for all but 37% of tropospheric air to diffuse into the stratosphere) (Callahan et al., 1979), <0.1% of tropospheric copper aerosol will be transported to the stratosphere.

The aquatic fate and transport of copper depends on the pH of water, its redox potential and the availability of other ions, ligands or sorbents present in water. Gibbs (1973) reported that most of the copper present in river water was present in the crystalline sediments (74-87%). The author defined the crystalline portion of the sediment to be that portion that did not release copper after extraction with $MgCl_2$ solution, reduction with sodium dithionite, and oxidation with sodium hypochlorite. The remaining copper was present in solution, as organic complexes, in the adsorbed state, in the precipitated and coprecipitated states and in inorganic solids. The maximum mobile part was present in the precipitated and coprecipitated states. The speciated inorganic copper in lake water of pH 7-9 was the following:

$$Cu(OH)_2 >> CuCO_3 > [Cu(CO_3)_2]^{2-} > CuCl_2 > [Cu(OH)]^+ > CuSO_4 \sim [Cu_2(OH)_2]^{2+} > [CuCl]^+ > [Cu(OH)_4]^{2-}$$ (Sanchez and Lee, 1978).

At pH >7 and in oxidizing environmental conditions, the controlling speciated form of copper may be $Cu_2CO_3(OH)_2$ rather than $Cu(OH)_2$ and $CuCO_3$ (Lu and Chen, 1977). In a reducing medium, the primary chemical form may be CuS (Lu and Chen, 1977). The major soluble complexes (both organic and inorganic) of copper under both oxidizing and reducing conditions were also determined by these authors (Lu and Chen, 1977). In acidic water (pH 4.6-5.7), the major copper species may be aquated Cu (II) ion. Other species, such as $CuCO_3$ and Cu-organic complexes were also present (Sposito, 1981). Therefore, acidification of aquatic media will increase the mobility of copper in such environments.

The fate of copper with respect to its leachability in purely organic spruce forest soils was studied by Tyler (1978). Appreciable mobilization of copper occurred only with prolonged leaching at pH 2.8. Therefore, it does not appear likely that acidic rainfall will result in significant mobilization of copper from organic soils unless the pH of rainfall decreases to <3. These authors estimated that ~50% of copper in the top few centimeters of these soils was organically bound, ~18% was in the hydroxy-carbonate form, ~7% was in the adsorbed state, ~11% was bound by other anions and 6% was irreversibly adsorbed. Only 3% of the copper was extractable with water at pH 4.5; hence only 3% was mobile at this pH. These authors speculated that in urbanized areas the effects of land clearing, profile disruption and increased acid rainfall may increase copper mobilization in these soils.

6. Environmental and Exposure Levels

6.1. ATMOSPHERIC LEVELS

The atmospheric concentrations of copper are dependent upon the contribution of the emission sources in a particular area. As noted previously, these levels are highly dependent upon localized conditions and vary from one locale to another. Based on the varying concentrations, it is logical to divide the atmospheric levels into four categories: remote, rural, urban and suburban, and hot spots (defined as the areas within the heavy dust fall-out ranges of smelter or ore processing sites). Besides these ambient atmospheric levels, the level of copper in occupational settings will also be discussed briefly as it pertains to the scope of this document.

6.1.1. Remote Areas

The atmospheric concentrations of copper in remote locations are important in that such data can serve as comparison background concentrations. These are useful to view to gain an idea of anthropogenic contributions of copper to the total atmospheric burden. The concentrations of copper in several remote locations (middle of ocean, mountain tops, etc.) were measured and found to vary from a low value of 0.01 ng/m^3 at Chacaltraya Mountain, Bolivia to a high value of 12 ng/m^3 at the North Indian Ocean (Nriagu, 1979). The median concentration of copper in these remote locations sampled during the late 1960's and early 1970's was 0.4 ng/m^3. Since local soils or crustal rocks should contribute to the atmospheric copper levels in remote locations, the enrichment factor for these aerosols is expected to be close to unity; however, the measured enrichment factors exceeded unity in almost all cases and were several hundred times higher in a few instances, indicating the substantial contribution from external sources other than background (e.g., aerial transportation) to the total atmospheric burden of copper, even at these remote locations.

6.1.2. Rural Areas

The atmospheric concentrations of copper in rural locations ranges from 5-50 ng/m^3 (Nriagu, 1979). Dorn et al. (1976) measured the atmospheric copper concentration at ~10 ng/m^3 at a rural farm in Southeast Missouri. The concentration of copper in aerosols from rural locations in Norway and Sweden was reported to range from 2.3-4.6 ng/m^3 (Lannefors et al., 1983). Stevens et al. (1980) reported the mean concentration of copper in aerosols from the Great Smoky Mountains, TN, to be <8 ng/m^3 and Lioy and Daisey (1983) reported a mean copper concentration of 10 ng/m^3 at Ringwood State Park, NJ (lightly populated and free of major local sources).

6.1.3. Urban and Suburban Areas

Pertinent data regarding the atmospheric levels of copper in urban and suburban areas in the United States are available from a number of sources (McMullen et al., 1970; Lee et al., 1972; Hammerle et al., 1973; Moyers et al., 1977). From these references, the United States atmospheric copper

level ranges from 30-200 ng/m^3, with the level of copper in urban air being 2-10 times higher than in rural air (Nriagu, 1979). A summary of the atmospheric levels of copper in United States urban and suburban locations, as measured by the National Air Surveillance Networks (U.S. EPA, 1976b) is given in Table 6. The mean copper concentrations at urban and suburban locations in the United States between 1970 and 1974 are 160 and 190 ng/m^3, respectively. The atmospheric copper levels in the United States have not changed and may have remained constant between 1965 and 1974 (Nriagu, 1979). The introduction of various clean air regulations in the United States since the late 1960's has resulted in an ~20% reduction in airborne particulates from 1970-1974; particulate emissions for several elements including arsenic, cadmium and zinc were reduced by this amount (Nriagu, 1979). During the early 1970's, however, copper followed a different trend.

Data regarding the United States atmospheric concentrations of copper in the early 1980's are limited. The measurement of atmospheric copper levels in three urban areas in NJ (Camden, Newark and Elizabeth) from 1981-1982 showed a range between 17 and 33 ng/m^3 with a mean value of 25 ng/m^3 (Lioy and Daisey, 1983). Similarly, the atmospheric copper level in Houston, TX, in 1980 was ~30 ng/m^3 (Dzubay et al., 1982).

Reports on the seasonal variations in atmospheric copper concentrations are conflicting. While some authors have reported high concentrations in summer and low concentrations in winter at certain locations, other authors have observed the opposite trend in other locations (Nriagu, 1979). This illustrates that the atmospheric level is more dependent on source than on seasonal variation. The burning of fossil fuels for heating during the winter may cause an increase in copper concentration in certain locations. The increased dispersion of street dusts in the atmosphere during the summer months may enhance copper concentration in certain locations (urban); however, the U.S. EPA (1976) study on copper levels during the summer and winter months for many urban and rural locations showed no consistent seasonal trend between 1970 and 1974.

6.1.4. Hot Spots

This term is being used to describe specialized areas located near processing plants. These areas have higher atmospheric levels of copper. For example, the median copper concentration in Sudbury, Ontario, was 371 ng/m^3 prior to the installation of a tall stack. After this installation, the median copper concentration decreased to 120 ng/m^3 (Nriagu, 1979). The typical copper concentration in the plumes from several copper smelters in Southeastern Arizona varied from 2000-9500 ng/m^3 compared to an average background level of 170 ng/m^3 (Small et al., 1981). The mean concentration of copper near a lead smelter in Kellogg, ID, was reported to be 186 ng/m^3. The smelting operation increased the concentration of copper in grass from a background level of 21-26 ppm to 38-110 ppm (Small et al., 1981). The mean copper levels near two secondary lead refineries in Toronto were reported to be 340 and 820 ng/m^3 (Paciga and Jervis, 1976). Therefore, the highest air concentration of copper in the United States will be localized and dependent upon industrial operations in that area.

6.1.5. Occupational Levels

The primary sources of occupational exposure to copper are ore smelting and related metallurgical operations, welding, handling of copper in metalwork and polishing operations (Stokinger, 1981). The health effects of industrial exposure to copper in a Norwegian copper plant, a Swedish

Table 6. **Summary of Atmospheric Copper Concentrations in United States Urban and Suburban Locations During the Period 1970-1974***

Year	Number of Observations	Copper Concentration (ng/m^3)		
		Range	Mean	Median
		Urban Locations		
1970	790	<1-1510	150	100
1971	715	<1-1560	180	110
1972	706	<1-1570	160	100
1973	555	<1-1440	150	100
1974	590	<1-1330	170	120
		Suburban Locations		
1970	124	1-1195	158	81
1971	96	14- 880	205	150
1972	137	1- 812	178	116
1973	99	11- 983	196	138
1974	78	23-1147	208	147

*Source: U.S. EPA, 1976b

plant handling copper sheeting and in other instances have been described by Stokinger (1981); however, the breathing zone copper levels were not reported for these occupational situations.

The occupational concentration of copper in a western copper smelter was reported by Cant and Legendre (1982). The time-weighted average concentration in the worker breathing zone varied between 22,000 ng/m^3 (22 $\mu g/m^3$) at the nickel recovery plant and 487,100 ng/m^3 (487 $\mu g/m^3$) at a converter furnace area. The level of copper fumes for stainless steel welders at a petrochemical plant was reported by Wilson et al. (1981). The mean concentration of copper around a maintenance shop area was reported to be 3000 ng/m^3 (3 $\mu g/m^3$); however, personal monitoring data based on time-weighted average concentrations from welding operations performed in confined spaces (distillation towers, reactors, etc.) showed a much higher mean copper concentration of 512,000 ng/m^3 (512 $\mu g/m^3$).

6.2. Water Levels

Data regarding the concentrations of copper in United States drinking water have been reported in several sources (U.S. EPA, 1980b, 1985; Sandhu et al., 1975, 1977; Page, 1981; Sharrett et al., 1982). Depending on the plumbing system, pH and hardness of water, copper concentration in drinking water may vary from a few $\mu g/l$ to >1 mg/l (Piscator, 1979). A combination of low pH, and soft water passing through copper pipes and fittings may produce the high copper levels in drinking water; however, only a little over 1% of United States drinking water exceeds the drinking water standard of 1 mg/l, with the average copper concentration in drinking water reported as ~0.13 mg/l (U.S. EPA, 1980b).

Copper concentrations in surface water vary worldwide from 0.5-1000 $\mu g/l$ with a median of 10 $\mu g/l$ (Davies and Bennett, 1983). The background concentration of copper in the U.S. surface waters is <20 $\mu g/l$. Higher concentrations of copper are usually from anthropogenic sources (U.S. EPA, 1980b). The levels of copper in sea water range from 1-5 $\mu g/l$ (Davies and Bennett, 1983). Further details regarding the levels of copper in drinking and surface water are reported in U.S. EPA (1980b, 1985).

6.3. Food and Dietary Levels

Pertinent data regarding the levels of copper in different foods are available from several sources (U.S. EPA, 1980b; NAS, 1977; Underwood, 1973, 1977). A general range of copper concentration in foodstuff is 0.1-44.0 $\mu g/g$ (wet weight). Crustaceans, shellfish, organ meats, dried fruits, legumes and nuts are particularly rich in copper, with copper contents ranging from 20-400 $\mu g/g$ (dry weight) (Underwood, 1977; NAS, 1977).

Studies conducted between 1930 and 1970 on the dietary intake of copper generally concluded that the typical U.S. diet provided an intake of at least 2 mg/day of copper, the level that is considered to be adequate for normal copper metabolism (Andelstein et al., 1956). Tompsett (1934) reported that the typical daily intake of copper from food appeared to be 2-2.5 mg/day. The reported average intake of copper by young children was 1.48 mg/day (Daniels and Wright, 1934).

6.4. Exposure

6.4.1. Inhalation

For comparison purposes, the inhalation exposure to copper has been derived based on the average copper concentrations in rural (see Section

6.1.2.) and urban and suburban (see Section 6.1.3.) atmospheres and using an adult inhalation rate of 20 m^3 air/day (Table 7). The mean copper concentration in hot spots has been derived from its concentration values measured in three such spots (see Section 6.1.4.). These values are used to show the relative difference in copper exposures in the four areas, and should not be considered as any type of average copper exposure. Additionally, these estimates are for copper and do not consider mixed exposures to additional compounds.

An increased intake of copper may occur as a result of other environmental media. Children who eat paint, dirt or clay, smokers and individuals who spend more time outdoors near high fallout areas are likely to experience increased exposures to copper (Hartwell et al., 1983). As in the case of a few other heavy metals (Hartwell et al., 1983), hair may be an easily accessible indicator of increased body burden. The relationship between increased body burden and enhanced levels of copper in hair has limitations, but has been demonstrated for occupational situations where copper-exposed workers had 706 μg/g of copper in hair compared to a 9 μg/g level for a control group (Finelli et al., 1984).

Table 7. Inhalation Exposure to Copper for Populations at Different Locations

Location	*Mean Concentration (ng/m^3)*	*Daily Inhalation Exposure[a] (μg)*
Rural	*25[b]*	*0.5*
Urban	*160*	*3.2*
Suburban	*190*	*3.8*
Hot spots	*449[c]*	*9.0*

[a] *Based on an inhalation rate of 20 m^3 air/day.*
[b] *The mean concentration is assumed to be an intermediate value for the concentration range of 5-50 ng/m^3.*
[c] *The mean concentration for hot spots has been derived from the concentration values measured in three spots (186 ng/m^3 for Idaho, 340 and 820 ng/m^3 for Toronto) given in Section 6.1.4.*

6.4.2. Ingestion

Assuming a daily consumption of 2 l of water with a mean copper concentration of 0.13 mg/P (see Section 6.2.), the daily intake of copper through drinking water is ~260 μg.

The average daily dietary intake of copper by an individual in the United States may range from <2 to ~4 mg (U.S. EPA, 1980b; Davies and Bennett, 1983). For ingestion, the dietary intake is, in general, an order of magnitude higher than intake from drinking water, except in rare cases of consumption of soft water which has been supplied by copper pipes. In the latter case, intake from drinking water may be as high as >2 mg/day based on the data of Piscator (1979).

6.5. Contribution of Inhalation to Total Exposure to Copper

In order to achieve a perspective of the levels of copper exposure from the inhalation route, this section utilizes the estimates from the previous sections of this chapter. As illustrated in Table 7, the daily inhalation exposure of the general population to copper would be in the range of 0.5-3.8 μg/day. For those individuals living in the immediate vicinity of a major copper

emitting source, the exposure would increase to ~9.0 μg/day. This values does not include those individuals with a combined exposure from living in the area and working in the processing facility. That exposure could vary greatly depending upon the plant area which the worker is employed, as well as the personal protective equipment used. In comparison, the average daily intake of copper through drinking water is ~0.26 mg/day, and may in ~1% of the cases exceed 2 mg/day (see Section 6.4.2.). The intake of copper in the diet is 2-4 mg/day (see Section 6.4.2.), and represents the major source of copper intake for the majority of individuals in the United States. In ~19% of the exposure cases, the intake of copper from drinking water will be comparable to its dietary intake.

The International Commission on Radiological Protection (ICRP, 1975) estimated that the daily intake of airborne copper based on the average copper concentration in air is ~0.02 mg/day for a 70 kg reference human. This indicates that inhalation of air containing background levels of copper would contribute negligible amounts (<1%) to the average daily intake of copper and would have little, if any, impact on the overall copper body burden. Davies and Bennett (1983) estimated that the inhalation pathway will contribute no more than 0.15 μg/kg to a total copper body burden of ~800 μg/kg. Using a high value of a range of median concentrations for copper in ambient air, the U.S. EPA (1985) estimated that atmospheric copper contributes no more than 1% to the total daily copper intake. Given that the above data are estimates, it is still very apparent that exposure from ambient atmospheric copper concentrations represents a very minor fraction of total individual copper exposure.

7. Terrestrial and Aquatic Effects

Significant quantities of copper can be deposited in areas downwind from smelters or other copper-emitting industries. Copper can accumulate to very high levels in soils and plants in these areas (Hutchinson, 1979), causing direct effects on terrestrial ecosystems. Runoff from affected terrestrial areas and direct atmospheric deposition may also contribute significant copper loadings to aquatic ecosystems (Hutchinson, 1979; Demayo et al., 1982). Possible consequences of these copper inputs will be discussed in this chapter.

7.1. Terrestrial Ecosystems

Adverse effects in terrestrial ecosystems occur as a result of atmospheric deposition from copper and other smelters; however, since smelter emissions contain a variety of toxic substances beside copper, it is difficult to attribute these effects to atmospheric copper deposition alone (Hutchinson, 1979).

In soils exposed to atmospheric deposition, high levels of copper and other metals may occur that can be directly toxic to certain soil microorganisms and can disrupt important microbial processes in soil, such as nutrient cycling. Hutchinson (1979) summarized several studies concerning heavy metal effects on microbial and fungal activity in soils, and found that copper and other metals inhibited mineralization of nitrogen and phosphorus in contaminated forest soils. Regression analysis indicated that copper was more important than other metals in controlling these processes. Hutchinson (1979) also cited studies that reported lower fungal species diversity in soils contaminated with heavy metals; copper was found to be more toxic to these species than other metals. This evidence suggests that while other metals in contaminated soils contribute to the observed effects, copper may be the most important in terms of toxicity.

Certain plant species (e.g., lichens and mosses) are especially sensitive to copper. High levels may cause elimination of sensitive species and selection for resistant ones, thereby changing community composition and species diversity. These effects have been observed in areas near smelters in Arizona, Pennsylvania, Ontario and Sweden (Hutchinson, 1979). In general, vegetation is completely devastated near the smelter, with a gradient of increasing species abundance and diversity radiating outward with the more tolerant plant species appearing closest to the smelter.

Some plants accumulate copper at high levels, with low-growing grasses generally having the highest concentrations and tree foliage the lowest. The major route of uptake appears to be from soil rather than direct atmospheric deposition (Hutchinson, 1979), since copper is unlikely to be transported across leaf cuticles. Radishes grown in controlled environments in soils taken from areas of atmospheric deposition exhibited elevated copper levels. Plants grown on soils from areas closest to smelters exhibited decreased growth, but growth was improved by addition of lime, presumably because higher soil pH decreased metal solubility and uptake (Hutchinson, 1979). Davis and Beckett (1978) reported decreased yields of lettuce, rape, wheat and ryegrass grown in sand culture with nutrient solutions containing 1.1-1.4, 0.3-2.8, 1.3 and 2.0 mg Cu/l, respectively. Decreased plant yields and/or elimination of important species in the food chain due to copper toxicity would result

in a decreased food supply for herbivore populations and man in the case of crop species.

Aside from the potential decrease in food supply, there has been little documentation of effects of atmospheric copper on wildlife. Some effects on domestic animals have been reported, however. Ruminants, especially sheep, are sensitive to copper poisoning (Gooneratne et al., 1980; Underwood, 1977). Describing chronic copper toxicity in sheep, Ishmael and Gopinath (1972) reported that copper accumulated in the liver for several weeks or months, followed by the sudden onset of severe hemolytic effects. Liver lesions developed progressively in the prehemolytic phase. Gracey et al. (1976) reported high SGOT enzyme levels, indicative of hepatic damage, and slightly elevated renal and hepatic copper levels in sheep grazed on copper rich grassland. No deaths from chronic copper exposure (during grazing season) occurred over a 3-year period during which a total of 47 kg Cu/ha was applied to the area. Theil and Calvert (1978) reported the development of massive hemolysis with high levels of copper in the liver, kidney and plasma in sheep treated orally with 20 mg $CuSO_4 \cdot 5H_2O$/kg bw/day (copper sulfate) within 7 weeks. The excess copper caused an increase in the concentration of iron in the plasma and spleen, possibly by interfering with iron metabolism and binding. Hepatic damage was observed in three histopathological studies of sheep chronically exposed to copper. King and Bremner (1979) fed sheep diets containing 29 ppm copper for 24 weeks; Wilhelmsen (1979) gave sheep daily doses of 4600 mg/day in food; and Gooneratne et al. (1980) administered oral doses of 20 mg/kg/day, 5 days/week for 48 days. Hepatic changes in these studies consisted of necrosis, hepatocyte swelling and significant increases in lysozyme content. Gopinath et al. (1974) also reported kidney effects (copper accumulation, proximal tubule degeneration and necrosis) in sheep developing copper-hemolysis after receiving copper sulfate at doses of 20 mg/kg/day for up to 10 weeks.

Incidents of chronic copper poisoning in sheep generally have occurred in areas of high copper levels in soils where sheep graze on plants that tend to concentrate copper (Underwood, 1977). In ruminants, relatively low copper levels in the diet ($<$16 mg/kg) may cause toxic effects if the molybdenum content of the food is low, while a high level of molybdenum in the diet may cause copper deficiency (Friberg et al., 1979). Although no such incidents have been reported in wildlife, it is reasonable to assume that chronic copper poisoning can affect those species as well. To the extent that atmospheric inputs increase copper levels in soil and vegetation, and may disrupt the food chain, they have the potential to affect wildlife populations.

7.2. Aquatic Ecosystems

It is likely that atmospheric sources contribute significant amounts of copper to certain bodies of water, especially those that lie downwind from industrial regions (Critchley, 1983; Demayo et al., 1982; Nriagu, 1979). The possible ecological and toxicological effects of copper in aquatic ecosystems must therefore be addressed; however, a detailed review of the literature is beyond the scope of this document. For ambient water, the reader is directed to U.S. EPA (1980b); for drinking water, an excellent review can be found in U.S. EPA (1985).

U.S. EPA (1980b) thoroughly summarized the information that was available at that time and drew several conclusions. The acute toxicity of copper to aquatic organisms is greatly affected by water chemistry, the toxicity decreases with increasing hardness and alkalinity. Apparently, chronic toxicity is not strongly affected by these parameters, however. Some of the

more sensitive aquatic species comprise daphnids, scuds, midges (chironomids) and snails, which are important food organisms for fishes (U.S. EPA, 1980b). Elimination of these organisms could result in decreased fish production if alternative food sources were not available. Elevated copper concentrations could also be directly toxic to fish, resulting in elimination of desirable sensitive species (e.g., salmonids) and possible replacement by less desirable resistant species. A large volume of laboratory data concerning the toxicity of copper to a variety of aquatic species was tabulated and summarized by U.S. EPA (1980b). These data are highly variable because of differences in test conditions (water chemistry, temperature, form of copper and life stage of organism that was used) that greatly influence copper toxicity. Because of the variability in toxicity due to environmental conditions, it is difficult to relate laboratory results to field situations. It would therefore not be useful to present these data in this report. In general, however, lab studies indicate that 0.005-0.015 mg Cu/l is a NOAEL for several aquatic animal species (U.S. EPA, 1976). Although copper sulfate has been used to control nuisance aquatic plants in ponds, no adverse effects on aquatic plant species were reported at concentrations lower than this. Additional data in the more recent literature did not contradict this level. U.S. EPA (1980b) concluded that the ambient water quality criteria to protect aquatic life is 0.0056 mg/l for freshwater species and 0.0040 mg/l for saltwater species, expressed as a 24-hour average of total recoverable copper.

Some of the field studies concerning effects of copper on aquatic ecosystems were summarized by Demayo et al. (1982). Shifts in fish and invertebrate community structure occurred in streams that were experimentally polluted with copper. Sensitive insect species such as *Psephenus* (beetle), *Baetis* sp. and *Stenonema interpunctatum* (mayflies) disappeared, and the community was dominated by chironomids (midges) when copper concentrations exceeded 0.052 mg/l. Fish community structure changed, probably as a result of impaired reproduction or movements of sensitive species.

7.3. Conclusions

Elevated copper concentrations can affect both terrestrial and aquatic ecosystems, causing changes in community structure and nutrient cycling. In most cases, however, atmospheric copper inputs alone are not large enough to cause substantial ecological effects. The worst case examples of the influence of copper on terrestrial and aquatic ecosystems are those near processing plants in the areas termed hot spots. In these areas, species diversity has been drastically changed. A full study on the food chain effects has not been documented.

8. Pharmacokinetics and Mammalian Toxicology

8.1. Pharmacokinetics

8.1.1. Absorption

Limited data are available regarding the absorption of inhaled copper or copper compounds. Copper-containing granules in the lung, liver and kidney have been observed in vineyard workers exposed during spraying of Bordeaux Mixture (an aqueous solution of lime and 1-2% copper sulfate used to control mildew on grapes) (Villar, 1974; Pimental and Menezes, 1975). Workers exposed to copper dusts and/or fumes have exhibited signs of metal fume fever (MFF) or "brass-founders' ague," an occupational disease characterized by malarialike symptoms (Gleason, 1968; Armstrong et al., 1983; Finelli et al., 1984). This is indirect evidence that copper can be absorbed through the lungs. Pulmonary absorption of copper has been reported in rats exposed to 50-80 mg/m^3 of a copper oxide aerosol (Batsura, 1969). Copper oxide crystals were observed to migrate across the air-blood barrier in the lung and were found in the plasma 6 hours after exposure. Davies and Bennett (1983) estimated that in humans only 20% (based on 50% absorption of the fractional amount retained in the lungs) of inhaled copper is eventually absorbed through the lung. Another 20% is retained in the lung tissue, while the remainder is probably removed by the bronchial mucosa (Davies and Bennett, 1983). The mechanism of copper absorption in the lung is unknown at this time.

Copper absorption in mammals after oral administration occurs primarily in the upper gastrointestinal tract (Evans, 1973) and is apparently regulated by the intestinal mucosa (Mason, 1979). At least two mechanisms serve to control GI absorption of copper (Gitlan et al., 1960; Crampton et al., 1965), an energy-dependent process involving the absorption of copper-amino acid complexes (Kirchgessner et al., 1967) and an inducible carrier protein mechanism that presumably involves binding to metallothionein (Mason, 1979; Evans, 1973; Sternlieb, 1980; Evans and Johnson, 1977). Absorbed copper is predominantly bound to albumin and is transported in the plasma where peak concentration levels are reached 1-3 hours following ingestion. Absorption of dietary copper can be affected by a number of factors, including competition with other metals (e.g., cadmium and zinc) for binding sites (Ogisu et al., 1974, 1979; El-Shobaki and Rummel, 1979; Fischer et al., 1981), nutritional status (Kirchgessner et al., 1973; Krishnamachari, 1974; Sandstead et al., 1979; Harmoth-Hoene and Schelenz, 1980; Miller and Landes, 1976), and treatment with other substances such as oral contraceptives (Onderka and Kirksey, 1975), carbon tetrachloride (Tichy and Cikrt, 1976), chelating agents (Forth et al., 1973) and a variety of other chemicals (Pleho, 1979; Moffitt et al., 1972).

Although estimates of the percentage of orally absorbed copper in humans vary widely, more recent studies have reported a figure of ~50% for general assessment with a range of 32-70% for adults (Strickland et al., 1972; King et al., 1978; Davies and Bennett, 1983) and 42-85% for children 3-6 years of age (ICRP, 1975). Since absorption (as well as other kinetic processes) of copper is governed by homeostatic mechanisms, the percentage of absorbed copper would be expected to be greater when the body stores are

depleted and ambient concentrations are low, and would be expected to be significantly less when the body stores are adequate and the dietary copper concentration is high. Data on rates of copper absorption in human tissue could not be located in the available literature.

Copper is also reportedly absorbed through burned skin when applied as copper sulfate during debridement procedures (Holtzman et al., 1966) and through intact skin as bis(glycinato)-copper (II) (Walker et al., 1977). In rats, absorption occurred from copper wire (Oreke et al., 1972) or a copper intrauterine device (Oster and Salgo, 1977) implanted in the uterus as a spermicidal contraceptive agent. In addition, elevated fetal copper levels indicate that copper can cross the placental barrier to be absorbed by the fetus.

8.1.2. Distribution

Following absorption, copper is loosely bound to albumin and amino acids and is transported to the liver, the main storage organ for copper. Once in the liver, copper is either retained, excreted into the bile or incorporated into ceruloplasmin, an α-globulin, which represents ~90% of the serum copper (Sternlieb et al., 1961; Underwood, 1977; Stokinger, 1981). Copper can also be released for incorporation into several copper-dependent enzymes or for the synthesis of erythrocuprein, a superoxide dismutase, which accounts for 60% of the copper present in red blood cells (Shields et al., 1961). Because copper is tightly bound to ceruloplasmin, the albumin and amino acid-associated copper complexes are responsible for copper distribution to and uptake from various tissues. Ceruloplasmin functions as a major regulator of copper retention and storage and represents an important homeostatic mechanism for controlling copper levels in the body (Underwood, 1977; Stokinger, 1981).

The total body copper content in a representative 70 kg man is estimated to range from 70-120 mg (USEPA, 1980b; ICRP, 1975; Stokinger, 1981; Underwood, 1977) of which ~33% is present in the liver and brain and ~33% is found in muscle tissue (Williams, 1982). Smaller quantities are found in the kidneys and heart. Table 8 outlines the tissue levels measured in human adults in both normal subjects and in patients with Wilson's disease (see Section 9.2.). Levels of copper in whole blood, red blood cells, white blood cells, and serum in a normal individual reportedly are 89, 93, 20 and 108 μg copper/100 ml, respectively (Stokinger, 1981).

Copper distribution in the fetus is very different from distribution in the adult. Fetal copper concentrations have been found to increase 3- to 4-fold in the last trimester due in part to rapid tissue growth and the formation of liver stores (Shaw, 1973; Dauncey et al., 1977). Approximately 50% of the cooper found in a newborn is present in the liver as neonatal hepatic mitochondracuprein (Porter, 1966). At birth, the copper body burden in an infant is ~4 mg/kg compared with ~1.4 mg/kg in adults (Underwood, 1977). Furthermore, the liver in a newborn has a 6- to 10-fold higher concentration of copper than the adult liver (USEPA, 1980b). The liver of the newborn has concentrations of copper of ~30 mg/kg wet weight, but during the first year of life its level decreases to between 5 and 10 mg/kg wet weight (Friberg et al., 1979). Plasma copper and serum ceruloplasmin levels are low at birth (~33% of that found in adults), but increase rapidly as the liver begins synthesizing ceruloplasmin, so that by 3-5 months of age circulating copper concentrations are similar to those observed in older children and adults (Henkin et al., 1973; Schorr et al., 1958). This limited research suggests that infants could be especially susceptible to higher levels of copper intake before their copper homeostatic mechanisms are fully developed.

Table 8. Tissue and Body Copper Levels in Representative Adult Man[a]

Tissue/Body Part	Copper (μg/g Fresh Tissue)		
	Normal[b]	Normal[b]	Wilson's Disease
Liver	7.8	7.1	99.2
Kidney	2.8	1.66	36.2
Heart	3.8	1.90	3.2
Spleen	1.5	0.85	NR
Lung	1.5	1.10	NR
Muscle	1.2	1.25	1.2
Stomach	2.3	1.07	4.9
Intestine (large)	2.1	1.1	1.6
Rib	NR	0.4	NR
Long bone	2.9	1.19	31.0
Brain	5.4	NR	54.9
Nail	15.6	NR	16.4
Skin	0.80	NR	1.1
Adrenal	1.8	NR	2.4
Pancreas	2.4	NR	3.1
Testis	1.1	NR	NR
Ovary	1.7	NR	1.3
Cornea	3.8	NR	35.1
Cartilage	0.55	NR	1.8
Hair	23.4	NR	15.8
CS fluid	0.13	NR	0.15
Bile	2.6	NR	0.7

[a]Source: Stokinger, 1981
[b]Levels were determined several decades apart, which may account for the different values.
NR = Not reported

8.1.3. Metabolism/Homeostatic Control Processes

Upon entering the liver, the primary organ of copper metabolism (Evans, 1979), copper is initially bound to a 10,000 dalton protein (Terao and Owen, 1973), presumed to be a thionein (Evans, 1973). Other hepatic copper binding proteins have also been reported (Winge et al., 1975; Riordan and Gower, 1975; Evans et al., 1975) and the transcription of the genes for some of these (i.e., metallothionein) has been observed to be induced by the presence of copper (Winge et al., 1975; Premakumar et al., 1975; Durnam and Palmiter, 1981).

Copper bound to proteins in the liver will eventually reappear in the blood, in copper-dependent enzymes and in bile components (Terao and Owen, 1973). Ceruloplasmin is a major regulator of plasma copper (Broman, 1964; Owen, 1965). Through its synthesis and release, ceruloplasmin is able to help maintain copper balance in the body (USEPA, 1980b), as evidenced by plasma copper levels in pregnant women which are 2- to 3-fold higher than normal. This has been related to increased synthesis of ceruloplasmin and increased stores of copper in the maternal liver which may be associated with increased estrogen levels (Henkin et al., 1971; Markowitz et al., 1955; Scheinberg et al., 1954). Ceruloplasmin is presumed to release copper at, or within, the target cell membrane (Marceau and Aspin, 1973a,b; Owen, 1971), from which it is incorporated into cytochrome oxidase and other copper proteins (Hsieh and Frieden, 1975). Copper is required in hemoglobin formation, pigment formation, carbohydrate metabolism, tissue respiration (Van Ravensteyn, 1944), catecholamine biosynthesis (Ahmed et al., 1981), crosslinking of collagen and elastin (Rucker and Tinker, 1977; O'Dell et al., 1978) and cross-linking of hair keratin (Danks et al., 1972).

Copper metabolism is highly dependent on the presence of other metals, most notably zinc, cadmium, molybdenum and iron. Underwood (1979) reviewed the literature pertaining to the interactions between copper and several of these trace elements. Molybdenum, along with sulfate, can alter the copper status of animals by increasing urinary and biliary copper excretion (Underwood, 1979; NAS, 1977). Zinc and iron both antagonize the absorption of dietary copper in experimental animals probably by competing for binding sites in the stomach and duodenum. This results in lower hepatic and plasma copper concentrations (Demayo et al., 1982). High levels of cadmium in the diet also can inhibit copper uptake, plasma ceruloplasmin content, and hepatic copper levels while enhancing copper retention in the blood, heart and spleen. Mercury and silver also apparently interfere with copper distribution (Underwood, 1979; Demayo et al., 1982) without affecting uptake, while lead reportedly disturbs copper absorption leading to depressed plasma copper and ceruloplasmin levels (Underwood, 1979).

8.1.4. Excretion

Copper is removed from the body by being incorporated into the feces, urine, perspiration, saliva, hair, nails and menstrual fluid (Sorel et al., 1984). Fecal copper represents unabsorbed dietary copper in addition to copper excreted in the bile, the saliva and from the gastric and intestinal mucosa (Gollan and Deller, 1973). Approximately 50% of the daily ingested copper will pass directly to the feces, while ~25% will appear in the bile (ICRP, 1975; Stokinger, 1981; Williams, 1982). Daily fecal excretion amounts to ~2.4-3.5 mg in a reference man and represents >95% of total copper excretion (ICRP, 1975). Urinary excretion of copper in humans is estimated to account for only ~0.5-4.0% of the daily turnover (Mason, 1979; Dowdy, 1969). The ICRP (1975) estimated that in a reference man ~50 μg/day is

excreted in urine, 40 μg/day in sweat and 3 μg/day in the hair and nails. Copper is also lost in the female menses with estimated losses of 0.11-0.74 mg per menstrual period (Greger and Buckley, 1977; Leverton and Binkley, 1944; Ohlson and Daum, 1935). The ICRP (1975) reported menstrual copper loss to be ~0.55 mg per 28 days or 20 μg/day.

Underwood (1977) estimated that of the 2-5 mg copper ingested daily by adults, 0.6-1.6 mg (32%) is absorbed, while the remainder is lost from the body with the feces. The majority of the absorbed copper (0.5-1.3 mg) is excreted in the bile while only 0.01-0.06 mg appears in the urine. The ICRP (1975) reported that copper balance in a reference man is maintained by an average daily copper intake of 3.5 mg from food and fluids and 0.02 mg from airborne sources and average daily losses of 0.05 mg in the urine, 3.4 mg in the feces (unabsorbed copper and biliary excretions) and 0.07 mg by other routes (sweat, hair, and menstrual fluid). These reports indicate that humans have sophisticated homeostatic mechanisms involving absorption, distribution and excretion that are able to maintain a physiological level of copper in the body.

The mean retention time for copper, based on the body burden, intake rate and absorption fraction, was calculated to be ~40 days, which corresponds to a half-life of ~4 weeks (Davies and Bennett, 1983). A short biological half-life for copper, coupled with well-established homeostatic mechanisms (rate of absorption, ceruloplasmin synthesis and release), makes it apparent that in normal individuals, there is significant protection against excess copper accumulation as when daily intakes exceed daily requirements (USEPA, 1980b); however, there are special susceptible groups at risk to high levels of copper (see Chapter 9).

8.2. Mammalian Toxicology

Table 9 summarizes the various noncancer health effects of copper observed in experimental animals. Two recent inhalation studies reported the effects of 0.6 mg/m^3 copper chloride ($CuCl_2$) administered to rabbits 6 hours/day, 5 days/week for 4-6 weeks. Examination of lung tissue revealed no significant differences in phospholipid content or in the number of histological lesions between treated and control animals; the lungs from copper-treated animals appeared essentially normal. A statistically significant increase in the number of alveolar type II cells was observed (Johansson et al., 1984). Lundborg and Camner (1984) reported that the number of alveolar macrophages and the lysozyme concentration in lavage fluid from the lungs of rabbits treated as indicated above were similar to control animals. Averaging the dose to 24 hours/day, 7 days/week and assuming that 1.9 kg rabbits have an inhalation rate of 1.06 m^3/day, the daily dose is calculated to be 60 μg/kg/day (0.6 mg/m^{3}x6/24x5/7x1.06 mg^3/day ÷ 1.9 kg). Because these studies only involved examination of tissues directly exposed to copper, they are difficult to interpret when systemic toxicity resulting from inhalation exposure is of concern.

Pimental and Marques (1969) exposed a group of 12 guinea pigs to an atmosphere saturated with Bordeaux Mixture (aqueous solution of lime and 1.5% $CuSO_4$) 3 times/day for 6.5 months (duration of each exposure was not reported). Examination of the lungs of the exposed guinea pigs revealed micronodular lesions and small histiocytic granulomas. A daily copper exposure level cannot be derived from this study, nor can the effects of copper sulfate be separated from those due to the lime. Whether the exposure situation was analogous to that of vineyard workers also cannot be determined from the given information. In a German paper (Eckert and Jerochin, 1982), the researchers showed that inhalation of Bordeaux mixture (copper sulfate

aerosol) was responsible for the development of lung changes. Copper sulfate was the responsible agent. Transitory pulmonary effects have also been observed in dogs following short exposures to dusts of copper stearate and copper acetate (Stokinger, 1981).

The toxicity of copper in experimental animals has also been investigated using oral and intraperitoneal routes of exposure. Acute toxicity studies have demonstrated intraperitoneal LD_{50} values in mice ranging from 3.5 mg/kg for copper metal dust (Stokinger, 1981) to 8.7 mg/kg for $CuSO_4 \cdot 5H_2O$ (Jones et al., 1980). Rat oral LD_{50} values reportedly fall between 140 mg/kg for $CuCl_2$ and 960 mg/kg for $CuSO_4 \cdot 5H_2O$ (Stokinger, 1981).

Short-term (90 days) oral studies in swine and rats exposed to the equivalent of ~2-40 mg copper/kg/day have consistently demonstrated the accumulation of copper in several tissues as well as toxic effects mainly in the liver, kidneys, blood and gastrointestinal tract (see Table 9). Dose- dependent copper accumulation in the blood, spleen and liver was observed in rats fed 0-4000 ppm copper (as copper sulfate) in the diet for 4 weeks and was accompanied by dose-related decreases in food intake and weight gain (Boyden et al., 1938). Heavy copper deposition in the livers and kidneys and copper-induced histopathology in these organs were reported in rats given 100 mg/kg/day copper sulfate for 20 days (Rana and Kumar, 1978). Parenchymal degeneration and perilobular sclerosis were seen in the livers and tubular engorgement and necrosis were observed in the kidneys of these rats. Rats treated similarly exhibited significant decreases in skeletal growth and weight gain, as well as an altered hematological profile (Rana and Kumar, 1980).

Statistically significant increases in brain dopamine, norepinephrine and copper levels were observed in male albino rats treated daily for 21 days by intraperitoneal injection of 2 mg Cu/kg as cupric chloride (Malhotra et al., 1982).

Pigs maintained on diets supplemented with copper carbonate (600-750 ppm) or copper sulfate (250-425 ppm) for 48-79 days exhibited a variety of toxic effects including the gradual development of anemia, jaundice, hepatic necrosis, gastrointestinal hemorrhage and decreased weight gain (Suttle and Mills, 1966a,b). Kline et al. (1971) reported that pigs exposed to 100-500 ppm copper sulfate in the diet for 54-88 days had alterations in weight gain, reductions in hemoglobin and hematocrit and greater than normal hepatic copper levels compared with control animals.

In a subchronic study, Haywood (1980) noted that the liver and kidneys of rats treated with 2000 ppm copper (as copper sulfate) in the diet for 15 weeks experienced a triphasic response during the exposure period. The first stage was characterized by the accumulation of copper with some signs of cellular disruption followed by a second stage of severe hepatic and renal necrosis. The final phase was marked by decreasing copper content and regeneration of damaged tissue as the animals appeared to develop tolerance against the effects of copper.

Another subchronic study (Narasaki, 1980) reported significant copper accumulations in the liver, serum, brain and kidneys as well as depressed weight gain and hepatic necrosis in rats receiving daily intraperitoneal injections of 1.5 mg copper/kg as copper lactate. These effects are similar to those seen in animals exposed acutely to copper.

There are limited data concerning the chronic toxicity of copper in experimental animals. Heavy accumulation of copper was observed in the liver and kidneys of rats maintained for 16 months on a diet supplemented with 5000 ppm copper acetate (Howell, 1959). Similar depositions were seen in the liver and kidney as well as the brain and the large and small bowel in rats exposed to 1250 ppm cupric acetate monohydrate in the drinking

Table 9. The Toxicity of Copper in Experimental Studies in Mammals

Species/ Strain	Sex/No.	Duration of Exposure (days)	Route of Administration	Vehicle	Dose/ Exposure as Cu (mg/kg/ day)	Compound	Effect	Reference
Rats/NR	M,F/10	20	gavage	NR	40	$CuSO_4$	Necrosis of the kidneys and liver	Rana and Kumar, 1978
Rats/albino	M/10	20	gavage	NR	40	$CuSO_4$	Decreased weight gain and blood components	Rana and Kumar, 1980
Rats/NR	M/12	21	Intra-peritoneal	saline	2	$CuCl_2$	Increased brain dopamine and norepinephrine	Malhotra et al., 1982
Rats/white	F/2-4	28	oral	diet	21.3[a]	$CuSO_4$	Dose-dependent decrease in food intake and growth; increased blood, liver and spleen copper concentration	Boyden et al., 1938
	M/1-5				34.9[a]	$CuSO_4$		
					46.0[a]	$CuSO_4$		
					32.3[a]	$CuSO_4$	Rapid weight loss and death within 1 week	
Rabbits/NR	M/8	28-42	Inhalation	air	0.06[b]	$CuCl_2$	50% increase in volume density of alveolar type II cells	Johansson et al., 1984
Rabbits/NR	M/8	28-42	Inhalation	air	0.06[b]	$CuCl_2$	No change in lung lysozyme levels	Lundborg and Camner, 1984
Pigs/large white	F/6	47-60	oral	diet	108 ppm[c]	$CuSO_4 \cdot 5H_2O$	Growth depression after 14 days; gastrointestinal hemorrhages, jaundice, hypertrophy and cirrhosis of liver	Suttle and Mills, 1966b
Pigs/large white	F/6	48	oral	diet	6.4-15.4[d]	$CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$	Three groups of animals on different basal diets all developed anemia	Suttle and Mills, 1966b

Table 9. (continued)

Species/ Strain	Sex/No.	Duration of Exposure (days)	Route of Administration	Vehicle	Dose/ Exposure as Cu (mg/kg/ day)	Compound	Effect	Reference
Pigs/large white	F/12	49	oral	diet	22[e]	$CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$	Liver necrosis and hypochromic microcytic anemia	Suttle and Mills, 1966a
Pigs/Hampshire, Yorkshire	NR/8	54	oral	diet	3.2[f]	$CuSO_4 \cdot 5H_2O$	None	Kline et al., 1971
					6.1[f]		Decreased weight gain, decreased hemoglobin, hematocrit	
	NR/8	61	oral	diet	3.2[f]	$CuSO_4 \cdot 5H_2O$	No effect compared with control	
					5.5[f]		Reduced growth and hemoglobin levels	
Pigs/large white	F/6	79	oral	diet	2.6[e]	$CuSO_4 \cdot 5H_2O$	Slight weight increase; jaundice	Suttle and Mills, 1966b
Pigs/Hampshire, Yorkshire	NR/12	88	oral	diet	1.8[f]	$CuSO_4 \cdot 5H_2O$	Slight increase in average weight gain	Kline et al., 1971
					2.5[f]		None	
					2.9[f]		Slight increase in average daily weight gain	
Rats/NR	M/4	105	oral	diet	40[g]	$CuSO_4$	Liver necrosis through week 6 followed by regeneration	Haywood, 1980
Rats/Wistar	M/36	>160	Intraperitoneal	water	1.5	$Cu(C_3H_5O_3)_2$	Decreased growth rate; increased serum liver enzymes; altered kidney	Marasaki, 1980

Table 9. (continued)

Species/ Strain	Sex/No.	Duration of Exposure (days)	Route of Administration	Vehicle	Dose/ Exposure as Cu (mg/kg/ day)	Compound	Effect	Reference
Guinea pigs/NR	NR/12	198	Inhalation	air (hydrated lime)	saturated air[h]	$CuSO_4$ (Bordeaux Mixture)	Micronodular lesions and small histiocytic granulomas in the lung	Pimental and Marques, 1969
Rats/NR	M,F/NR	486	oral	diet	80[g]	$Cu(C_2H_3O_2)_2 \cdot H_2O$	Deposition of copper in the liver and kidneys functions	Howell, 1959
Rats/Sprague-Dawley	M/22	902	oral	drinking water	20.7[i]	$Cu(C_2H_3O_2)_2 \cdot H_2O$	Deposition of copper in the liver and kidneys	Owen, 1974

[a] These doses were calculated from reported daily food intakes for each exposure group using an average rat weight of 235 g which was derived from the daily food intake for control animals using the assumption that the rats consume food equivalent to 5% of their body weight. The high dose group had a severely restricted food intake that was partially responsible for the deaths observed in this group.

[b] Dose was calculated by multiplying copper concentration of 0.6 mg/m^3 by 5/7 and 6/24 to expand dosage to a 7-day week and 24-hour day, respectively, and by assuming that a 1.9 kg rabbit has an inhalation rate of 1.06 m^3/day. An absorption factor was not included.

[c] Daily dose cannot be calculated from reported data. The only information given was a starting pig weight of 17 kg.

[d] Dose calculated from weight and food intake data. The dose range was due to food intake levels of pigs on different basal diets (U.S. EPA, 1985).

[e] Dose calculated from weight and food intake data (U.S. EPA, 1985).

[f] Daily doses were calculated using the reported feed/weight gain ratio and the average of the reported weights before and after the exposure period for each treatment group.

[g] Assumes a rat consumes food equivalent to 5% of its body weight/day.

[h] Equivalent daily dose cannot be calculated from the available information.

[i] The daily intake of copper in a 300 g rat was reported to be 0.2 mg from 22 g food and 6 mg from 15 ml H_2O.

NR = Not reported

water for up to 902 days (Owen, 1974). Neither of these studies reported any other signs of copper toxicity, which limits their usefulness in assessing the hazard of chronic copper exposure.

8.3. Other Effects

8.3.1. Carcinogenicity

Bionetics Research Laboratory (BRL, 1968) studied the carcinogenicity of a copper-containing compound, copper hydroxyquinoline, in two strains of mice (B6C3F1 and B6AKF1) fed a diet that provided sufficient copper (i.e., 5.7 mg Cu/kg feed). The copper complex was administered orally and by subcutaneous injection. Using subcutaneous administration, groups of 18 male and 18 female 28-day-old mice of both strains were given a single injection of gelatin or 1000 mg copper hydroxyquinoline/kg bw (180.6 mg Cu/kg) suspended in 0.5% gelatin. The animals were observed until they were 78 weeks old, and then killed. Oral exposure consisted of similar groups of 7-day-old mice treated daily by gavage with 1000 mg copper hydroxyquinoline/kg bw (i.e., 180.6 mg Cu/kg) suspended in 0.5% gelatin until age 28 days, whereupon the compound was administered in the feed at a concentration of 2800 ppm (505.6 ppm Cu). Animals were fed the treated diet until they were 78 weeks old, at which time they were killed. Positive, negative, vehicle and untreated control animals were also maintained and compared with treated animals. All animals killed or found dead were subjected to routine macro-and microscopic histological analysis to identify tumor-bearing tissues. No statistically significant increases (with respect to controls) in the incidence of lymphatic leukemias, reticulum cell sarcomas, pulmonary adenomas or carcinomas, hepatomas, hepatic carcinomas, mammary carcinomas, skin carcinomas or cavernous angiomas were observed in orally-treated mice.

In the portion of the study using subcutaneous exposure, male B6C3F1 mice had an increased incidence of reticulum cell sarcomas compared with controls (e.g., 6/17 treated; 8/141 control; $p<0.001$). No tumors were observed in treated male B6AKF1 mice. Female mice of either strain had low incidences of reticulum cell sarcomas. Treated and control B6C3F1 females had incidences of reticulum cell sarcoma of 1/18 and 1/154, respectively. Treated and control B6AKF1 females had incidences of reticulum cell sarcoma of 3/18 and 5/157, respectively (BRL, 1968).

Gilman (1962) studied the carcinogenicity of cupric oxide, cupric sulfide and cuprous sulfide in 2-to 3-month-old Wistar rats. Groups of 30-32 rats were given single intramuscular injections containing 20 mg of cupric oxide (16 mg Cu), cupric sulfide (13.3 mg Cu) and cuprous sulfide (16 mg Cu) into the left and right thigh of each rat. All animals were observed for up to 20 months, after which histopathological evaluation was conducted. Controls were not reported. Of the animals receiving cupric oxide, cupric sulfate and cuprous sulfate, the ratios of animals surviving the experiment/animals dosed were 10/32, 19/30 and 18/30, respectively. No injection-site tumors were observed, and the groups of animals receiving cupric oxide, cupric sulfide and cuprous sulfide had 0, 2 (mammary fibroadenomas and reticulocytoma), and 1 (mammary fibroadenoma), respectively.

Crystalline CuS has been shown to induce DNA strand breaks in Chinese hamster ovary cells (Robison et al., 1982). In the study, the researchers found that water insoluble crystalline sulfide of copper induced considerable reductions in the molecular weight of DNA. Accordingly, these compounds are all actively phagocytosed by the ovary cells and thereby can have pronounced intracellular effects. The fact that some metal sulfides cause DNA strand breaks and reduce its molecular weight may account for the

ability of these compounds to cause cellular transformation (Robison et al., 1982). The effects of insoluble metal compounds have not been investigated. Haddow and Horning (1960) published a table of bioassay results on various copper compounds from which Table 10 was prepared; however, no experimental detail was provided. Data for determining the carcinogenicity of inhaled copper or copper compounds are not available. Some short-term tests have indicated that certain of the copper salts may have characteristics suggestive of carcinogens. However, the overall weight-of-evidence suggests that there is insufficient data to determine the carcinogenic potential at this time. Using the USEPA Guidelines for Carcinogenic Risk Assessment (USEPA, 1986), copper is in Group D: Not classifiable as to human carcinogenicity.

8.3.2. Mutagenicity

The available data obtained from *in vitro* mutagenicity assays do not provide sufficient evidence to form a conclusion regarding the mutagenicity of copper (Table 11).

A reverse mutation assay reported dose-related mutation in *E. coli* with 2-10 ppm copper sulfate (Demerec et al., 1951). More recently, Moriya et al. (1983) reported the absence of mutation in *E. coli* incubated with up to 5 mg copper quinolinolate/plate and in *Salmonella typhimurium* strains TA98, TA1535, TA1537 and TA1538. Copper 8-quinolinolate was mutagenic to *S. typhimurium* strain TA100, but only when a source of mammalian metabolic activation was included (Moriya et al., 1983). Up to 5 mg of copper sulfate/plate did not induce reverse mutations in *S. typhimurium* TA98 and TA100 either with or without metabolic activation.

Other investigators have obtained negative mutagenic results with copper sulfate or copper chloride in other microbial assays. These include *Saccharomyces cerevisiae* D-7 (Singh, 1983) and *Bacillus subtillis* (Nishioka, 1975; Matsui, 1980; Kanematsu et al., 1980).

Several isolated cell mutagenicity assays have produced positive results with copper compounds. Errors in DNA synthesis from poly(c)templates have been induced in viruses (Sirover and Loeb, 1976) when incubated in 20-150 mM $CuCl_2$ or $Cu(C_2H_3O_2)_2$. Casto et al. (1979) induced enhanced simian adenovirus cell transformation in Syrian hamster embryonic cells with the addition of 0.38 mM Cu_2S and to a lesser extent with 0.08 mM of $CuSO_4$. Single strand breaks in DNA in isolated rat hepatocytes were detected after exposure to 1.0 mM, but not 0.03 or 0.3 mM cupric sulfate (Sina et al., 1983). The authors suggest that this is false-positive because cytotoxicity was >30% and cell lysis would result in DNA fragmentation.

High concentrations of copper compounds have been reported to induce abnormalities at mitosis in rat ascites cells and recessive lethals in *Drosophila melanogaster*. Law (1938) reported increases in the percent lethals observed in *Drosophila* larvae and eggs when exposed to copper by microinjection (0.1% $CuSO_4$) or immersion (concentrated aqueous $CuSO_4$), respectively.

8.3.3. Teratogenicity and Reproductive Toxicity

Copper deficiency has been observed to produce teratogenic response in lambs, goats, rats, guinea pigs, dogs and chicks. Terata include neural degeneration, reduced growth, skeletal malformations and cardiovascular lesions (Hurley and Keen, 1979).

The spermicidal properties of copper are well known and were first demonstrated in the 19th century (Holland and White, 1982). Prevention of mammalian embryogenesis because of the small amounts of copper

Table 10. Tumorigenicity of Some Copper Compounds*

Agent Under Test	Number and Strain of Mice	Number of Weekly Subcutaneous Injections/ Dose	Months of Experiment to Date and Survivors	Tumors Recorded
Copper-dextran	20 stock	6/0.1 cc of 1 in 4 dilution	10 (13)	None
8-hydroxyquinoline copper complex	20 stock	39/0.1 mg	10 (14)	1 pleomorphic sarcoma
Cross-conjugated macrocycle copper porphyrin	20 stock	4/0.5 mg	10 (14)	None
Copper phthalocyanine	20 stock	34/0.5 mg	8 (17)	None
Copper phthalocyanine tetra-3-sulfonic acid	20 stock	36/0.5 mg	8 (20)	None
Copper phthalocyanine tetra-4-sulfonic acid	20 stock	25/0.5 mg	8 (11)	None

*Source: Haddow and Horning, 1960

Table 11. Mutagenicity Data for Copper Compounds

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA98, TA100	plate incorporation	≤ 5000 µg copper sulfate/plate	± rat liver S-9	-	NC	Moriya et al., 1983
Reverse mutation	S. typhimurium TA100	plate incorporation	0.5-10 µg copper 8-quinolinolate/ plate	+ rat liver S-9	+	NC	Moriya et al., 1983
Reverse mutation	S. typhimurium TA100	plate incorporation	0.5-10 µg copper 8-quinolinolate/ plate	- rat liver S-9	-	NC	Moriya et al., 1983
Reverse mutation	S. typhimurium TA98, TA1535, TA1537, TA1538	plate incorporation	≤ 5000 µg copper 8-quinolinolate/ plate	± rat liver S-9	-	NC	Moriya et al., 1983
Reverse mutation	S. typhimurium TA100, LT2	spot test (paper disc)	10 µl of 10^{-6} to 10^{-3} M aqueous solution of $CuCl_2 \cdot 2H_2O$	NA	-	NC	Tso and Fung, 1981
Reverse mutation	Saccharomyces cerevisiae D-7	spot test (center wall)	0.1 M copper sulfate	NA	-	NC	Singh, 1983
Reverse mutation	Escherichia coli WP2 hcr	plate incorporation	≤ 5000 µg copper 8-quinolinolate/ plate	NA	-	NC	Moriya et al., 1983
Reverse mutation	E. coli Sd-4	plate incorporation	2-10 ppm copper sulfate	NA	+	Dose related at ≥ 2 ppm	Demerec et al., 1951

Table 11. *(continued)*

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Growth inhibition (rec)	Bacillus subtilis H17, M45	spot test (paper disc)	0.05 ml of 0.05 M CuCl or $CuCl_2$ solution	NA	-	NC	Nishioka, 1975
Growth inhibition (rec)	B. subtilis N16 17, N16 45	liquid cultivation	16.5-18 mg copper sulfate/l	NA	-	NC	Matsui, 1980
Growth inhibition (rec)	B. subtilis H17, M45	spot test (paper disk)	0.05 ml of 0.001-10 M CuCl or $CuCl_2$ solution	NA	-	NC	Kanematsu et al., 1980
Errors in DNA synthesis	Avian myeloblastosis virus, DNA polymerase	liquid holding	20-150 mM $CuCl_2$ or $Cu(C_2H_3O_2)_2$	NA	+	NC	Sirover and Loeb, 1976
DNA single-strand breaks	rat hepatocytes	plate incorporation, then alkaline elution	0.03-0.3 mM cupric sulfate	NA	-	Elution rate ≥ 3 times the control rates	Sina et al., 1983
DNA single-strand breaks	rat hepatocytes	plate incorporation, then alkaline elution	1.0 mM cupric sulfate	NA	+	Elution rate ≥ 3 times controls rates, toxicity >30%	Sina et al., 1983

Table 11. (continued)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Cell transformation	Syrian hamster embryo cells by simian adenovirus SA7	plate incorporation	≥ 0.38 mM Cu_2S	NA	+	Enhancement ratio: Transformation frequency treated / Transformation frequency control = 16.2	Casto et al. 1979
Cell transformation	Syrian hamster embryo cells by simian adenovirus SA7	plate incorporation	0.08-0.64 mM $CuSO_4$	NA	+	Enhancement ratio = 2.2	Casto et al., 1979
Recessive lethals	Drosophila melanogaster Oregon-R	microinjection into larvae	0.1% $CuSO_4$	NA	+	1.06% lethals (0% in controls)	Law, 1938
Recessive lethals	D. melanogaster Oregon-R	immersion of eggs for 10 minutes	concentrated aqueous solution of $CuSO_4$	NA	+	1.25% lethals (0% in controls)	Law, 1938

Table 11. (continued)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Mitotic abnormalities	MTK-sarcoma III rat ascites	in vivo	150 mg copper sulfide/kg i.p.	NA	+	Chromatic aggregation stickiness contraction, scattering, lagging and clumping of chromosomes	Kumura and Makino, 1963
Mitotic abnormalities	MTK-sarcoma III rat ascites	in vivo	300 mg copper sulfate/kg i.p.	NA	+	Reversible events: lobated nuclei, karyorrhexis and multipolar spindle formation	Kimura and Makino, 1963

NA = Not applicable; NC = No comment

absorbed from intrauterine loops or wires fashioned from copper has been demonstrated (Oster and Salgo, 1977; Hurley and Keen, 1979).

The embryotoxicity and teratogenicity of i.v. injection of copper salts was first demonstrated in hamsters by Ferm and Hanlon (1974). Copper sulfate and copper citrate dissolved in demineralized water were both observed to reduce embryonic viability and produce abnormal offspring when injected into the lingual vein of pregnant dams on the 8th day of gestation. Day 1 of gestation was considered the day after which mating occurred. Administration of demineralized water alone produced no abnormal embryos (Table 12). Administration of copper sulfate (2.13 mg Cu/kg) to 16 dams caused the formation of 12 abnormal of 155 live embryos (five thoracic wall hernias, four encephalocoeles, two spina bifida and one microphthalmia). Similar administration of copper sulfate (at 4.25 mg Cu/kg) to three dams caused the development of four abnormal of seven live embryos (one exencephaly, one hydrocephalus, one abdominal hernia and one abnormal spinal curvature). Administration of higher doses of copper sulfate (7.5 and 10 mg/kg) resulted in 100% mortality of embryos and dams, respectively.

Copper administered in a chelated form (copper citrate) was observed to be a more potent teratogen than the uncomplexed form (copper sulfate). Administration of 0.25-1.5 mg Cu/kg (as citrate) to 13 dams resulted in the development of four abnormal of 172 live embryos (two tail defects, one microphthalmia and one cranioarchischisis). Similar administration of 1.8 mg Cu/kg to six dams produced 14 abnormal of 81 live embryos (13 tail defects and 1 meningocele). Administration of 2.2 mg Cu/kg to eight dams produced 35 abnormal embryos (25 tail defects, 6 thoracic wall defects, 2 microphthalmias, 1 abdominal wall defect and 1 facial cleft). Administration of 4.0 mg Cu/kg to two dams resulted in the death of both.

Experiments with ^{64}Cu nitrate injected into pregnant dams showed that with 0.55, 12.8, 0.53, 1.47 and 0.81 μg ^{64}Cu/g tissue in the maternal blood, maternal liver, uterus, placenta and embryo, respectively, copper permeates the hamster placenta (Ferm and Hanlon, 1974).

DiCarlo (1980) produced terata in hamsters by i.p. injection of copper citrate. Pregnant female Golden hamsters were given an i.p. injection of demineralized water either alone or containing 2.7 mg copper citrate/kg on the 8th day of gestation. The day after mating was considered day 1 of gestation. The control and dosed groups consisted of 37 and 89 animals, respectively. All dams were killed on the 12th or 13th day of gestation, whereupon all viable embryos were removed for histopathological analysis. Copper was not observed to affect maternal survival, but did reduce maternal body weight gain, possibly by inducing a high resorption rate. Control embryos were observed to be free of gross teratological effects, but on histopathological examination, 2 of 68 randomly-chosen embryos were observed to have cardiac muscular ventricular septal defects. Of the treated embryos, 45 of 855 embryos examined had gross malformations (e.g., limb and tail defects and edema). On histopathological examination, 58 cardiac defects (various ventricular septal malformations) were observed in 49 embryos with gross malformations. The author stated that copper's role as a prosthetic group in oxidative enzymes could lead to teratogenesis when present in excessive amounts by interfering with these metabolic reactions during organogenesis. However, the relevance of these studies is questionable because i.p. injection of a high level of copper does not duplicate any of the means whereby toxic levels might enter the body under normal environmental conditions.

Lecyk (1980) observed teratogenic effects in two strains of mice fed diets supplemented with copper sulfate before mating. Various numbers (see Table 12) of C57BL and DBA mice were maintained for 1 month on diets supplemented with 0, 500, 1000, 1500, 2000, 3000 and 4000 ppm copper

Table 12. Teratogenicity Data for Copper Compounds

Compound, Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days[a]	Observation Day	Maternal Response	Fetal Response			Reference
								Avg. Litter Size	Avg. Weight (g)	Malformations	
$CuSO_4$, oral	mouse/ C57BL	21	diet	0	30 to 0	19	NR	3.1	1.1	0	Lecyk, 1980
		10		25.9 mg Cu/kg/day[b]				4.6	1.3	0	
		18		51.7 mg Cu/kg/day[b]				4.5	1.2	0	
		7		77.6 mg Cu/kg/day[b]				4.4	1.1	0	
		10		103.5 mg Cu/kg/day[b]				4.2	1.2	0	
		22		155.3 mg Cu/kg/day[b]				2.5	1.0	1 skeletal	
		18		207.1 mg Cu/kg/day[b]				1.9	1.0	3 hernia, hydrocephalus, skeletal	

Table 12. *(continued)*

Compound, Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days[a]	Observation Day	Maternal Response	Fetal Response			Reference
								Avg. Litter Size	Avg. Weight (g)	Malformations	
$CuSO_4$, oral	mouse/ DBA	17	diet	0	30 to 0	19	NR	4.5	1.0	0	Lecyk, 1980
		10		25.9 mg Cu/kg/ day[b]				5.4	1.2	0	
		10		51.7 mg Cu/kg/ day[b]				5.1	1.2	0	
		14		77.6 mg Cu/kg/ day[b]				4.1	1.2	0	
		10		103.5 mg Cu/kg/ day[b]				4.1	1.1	0	
		18		155.3 mg Cu/kg/ day[b]				3.1	1.1	2 skeletal	
		20		207.1 mg Cu/kg/ day[b]				2.7	1.1	4 encephaloceles, skeletal	

Table 12. (continued)

Compound, Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days[a]	Observation Day	Maternal Response	Fetal Response			Reference
								Avg. Litter Size	Avg. Weight (g)	Malformations	
Copper citrate, i.p.	hamsters/ Golden	37	D.I. H_2O	0	8	12-13	NR	Free of gross teratogenic effects (0/455), 2/37 had abnormalities, 2/68 heart defects			DiCarlo, 1980
		89	D.I. H_2O	27 mg/kg			No effect on survival, but a 10% reduction in body weight gain.	45/855 fetuses with gross defects (limb, tail, edema) 19/89 litters had abnormalities, 58 ventricular septal defects in 49 fetuses			
$CuSO_4$, i.v.	hamsters/ Golden	10	D.I. H_2O	0	8	12-13	NR	92% viable embryos, 8% resorption, 0% abnormal			Ferm and Hanlon, 1974
		16		2.13 mg Cu/kg			NR	74% viable embryos, 26% resorption, 6% abnormal			
		3		4.25 mg Cu/kg			NR	14% viable embryos, 86% resorption, 8% abnormal			
		3		7.50 mg Cu/kg			NR	0% viable embryos, 74% resorption, 8% abnormal			
		2		10.0 mg Cu/kg			Death				

Table 12. (continued)

Compound, Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days[a]	Observation Day	Maternal Response	Fetal Response			Reference
								Avg. Litter Size	Avg. Weight (g)	Malformations	
Copper citrate i.v.	hamsters/ Golden	13	D.I. H_2O	0.25-1.5 mg Cu/kg	8	12-13	NR	83% viable embryos, 16% resorptions, 2% abnormal			Ferm and Hanlon, 1974
		6		1.8 mg Cu/kg			NR	59% viable embryos, 41% resorptions, 17% abnormal			
		8		2.2 mg Cu/kg			NR	66% viable embryos, 34% resorptions, 35% abnormal			
		2		4.0 mg Cu/kg			Death				

[a] Relative to day of conception (day 0)
[b] Assume mice consume 13% of bw/day

NR = Not reported

sulfate. These concentrations are equivalent to 0, 199, 398, 597, 796, 1195 and 1593 ppm Cu, respectively. Assuming that mice consume food at a rate of 13% of their body weight per day, doses at 199 and 398 ppm copper are equivalent to 25.9 and 51.7 mg Cu/kg/day, respectively. After 30 days of treatment, the females were mated with males of respective strains and the day on which a vaginal plug was observed was determined as day 0 of gestation. Pregnant mice were allowed to gestate until the 19th day, at which time they were killed and the fetuses were examined for morphological defects. Low doses (500-1000 ppm) of copper were observed to stimulate embryonic development; increased litter size and increased fetal weight resulted. Higher copper doses (>1000 ppm) increased fetal mortality and decreased litter size. When supplemented in the diet at 3000 and 4000 ppm, copper sulfate caused a level (2-8% of living fetuses) of various skeletal and other malformations that were absent at lower doses and controls. No abnormal fetuses were observed in control groups. However, the observations by Boyden et al. (1938) imply that food intake decreases at high concentrations of copper. Therefore, the actual food intake may have been seriously reduced, therefore adversely affecting fetal development.

8.4. Summary

Efficient homeostatic mechanisms generally protect mammals from the adverse effects of dietary copper deficiency or excess. With the exception of ruminant animals, the chronic toxicity of orally-administered copper has not been well investigated. An inborn error in copper metabolism in humans (Wilson's disease) may be the only form of chronic copper toxicosis in man (see Chapter 9).

Ingestion of 100 mg Cu/kg/day by rats for 1 week resulted in no observable adverse effects (e.g., no liver accumulation and no adverse renal or hepatic morphology). Administration of this dose for up to 6 weeks caused severe renal and hepatic effects in rats. Further administration of copper at this dose to rats for up to 15 weeks resulted in no further damage; rather, regeneration of hepatic and renal tissues was observed (Haywood, 1980). Support for these observations was reported by Rana and Kumar (1980) who observed liver and kidney necrosis in rats fed 25.4 mg Cu/kg/day for 20 days.

Increased liver copper concentrations were observed in rats fed 16.7 mg Cu/kg/day for 27 days (Boyden et al., 1938) and 11.0 mg Cu/kg/day for 21 days (Miranda et al., 1981). Administration of higher levels of dietary copper resulted in elevated liver and splenic copper levels, growth reduction and reduced dietary intake resulting in death (Boyden et al., 1938).

Malhotra et al. (1982) observed that rats given daily i.p. injections of 2 mg Cu/day had significantly ($p<0.05$) elevated levels of brain dopamine and norepinephrine when compared with controls.

Pigs appear to be more sensitive than rats to the acute toxicity of copper. Suttle and Mills (1966a,b) reported adverse effects in pigs given copper supplements in doses as low as 6.4 mg Cu^{+2}/kg/day for 48 days and 2.6 mg Cu^{+2}/kg/day for 79 days. Kline et al. (1971) reported beneficial effects of copper (as copper sulfate) supplementation in Hampshire and Yorkshire pigs (~24 kg) at doses of 1.8-3.2 mg Cu^{+2}/kg/day for 61-88 days. Administration of 5.5 mg Cu^{+2}/kg/day for 61 days caused adverse effects (e.g., growth reduction, reduced hemoglobin and increased hepatic copper) (Kline et al., 1971).

Liver damage, hemolytic anemia, renal damage and gastrointestinal irritation are effects of acute copper poisoning that have been observed to occur in laboratory animals and man (Bremner, 1979; Owen, 1981).

Equivocal results have been obtained from experiments designed to evaluate the carcinogenicity and mutagenicity of copper compounds. Administration of copper compounds to mice by subcutaneous injection has been reported to induce tumor formation (BRL, 1968; Haddow and Horning, 1960). The only tumorigenicity studies for orally-administered copper were negative (BRL, 1968).

Microbial mutation assays using copper compounds have generally provided negative results. Some mutagenic activity by copper compounds at high concentrations has been observed in cell culture assays. Copper sulfate was observed to increase the frequency of recessive lethal mutations in *D. melanogaster* at high concentrations (Law, 1938).

Copper compounds have been observed to elicit a teratogenic response at ~2 mg Cu/kg when injected into female hamsters on the 8th day of pregnancy (DiCarlo, 1980; Ferm and Hanlon, 1974). Lecyk (1980) reported a teratogenic response of orally-administered copper sulfate in mice for the 30-day dietary exposures at 103.5 mg Cu/kg/day. Copper deficiency has also been shown to produce teratogenic responses.

Pertinent data regarding the carcinogenicity, mutagenicity or teratogenicity of copper or copper compounds following inhalation exposure could not be located in the available literature. Data pertaining to the selective effects elicited by copper species of different valences also could not be located in the available literature. The studies reviewed in this chapter are concerned primarily with copper-related compounds, since data on elemental copper and health effects have not been located.

9. Human Health Effects and Populations at Risk

9.1. Human Health Effects

The noncancer health effects of airborne copper fumes, dusts or mists in humans result primarily from industrial exposures and are manifested predominantly by dermatologic and respiratory symptoms. Despite the fact that occupational exposure to copper and copper products is common, cases of copper intoxication are rare (Cohen, 1974; Williams, 1982). A condition known as "metal fume fever" characterized by influenza-like symptoms (stuffiness of the head, sensations of chills or warmth, general aches and pains) has been reported in workers exposed to fine copper dusts (~0.1 mg Cu/m^3) (Gleason, 1968), copper fumes (Armstrong et al., 1983) and copper oxide and copper acetate dusts (Stokinger, 1981; Cohen, 1974). In the Gleason (1968) study, the author noted that the data do not permit broad generalizations about the toxicological aspects of fine airborne copper dust; the purpose of the study was to justify exhaust control. The study design was very limited and high levels of aluminum from the polishing abrasive were found. Once exhaust fans were installed, the final air samples showed negligible amounts (<8 $\mu g/m^3$) of copper dust in the air. In general, the acute effects of copper intoxication are readily reversible since removal of the offending agent is usually the most effective treatment (Cohen, 1974). Chronic effects observed from industrial exposures to copper include contact dermatitis (Stokinger, 1981; Cohen, 1974; Williams, 1982), mild anemia (0.6-1 mg Cu/m^3) (Finelli et al., 1984) and leukocytosis (Armstrong et al., 1983). A study of 14,562 white male workers from the copper and zinc smelting industries did not show any overall mortality excesses as compared with the mortality of the total U.S. population (Enterline et al., 1986). In this study, there were only two disease associations of importance. Neither association involved copper *per se*; however, an association between arsenic exposure and lung cancer was found to be strong, even at low levels. The other finding was between sulfur dioxide exposure and emphysema mortality.

Reports of local and systemic effects in vineyard workers exposed to Bordeaux mixture (see Chapter 8) have revealed a potentially more serious consequence of inhaled copper. Two male vineyard sprayers reportedly had histological lesions in the lungs characterized by desquamation, intra-alveolar acrophages and inter-alveolar septal histiocytic granulomas (Pimental and Marques, 1969). These lesions were similar to those observed in guinea pigs exposed to Bordeaux mixture (see Chapter 8). Villar (1974) analyzed 15 cases of "vineyard sprayer's lung" and reported that dyspnea, weakness, decreased appetite, weight loss, radiographic opacities and copper deposits in the lungs were common symptoms. Copper-containing liver granulomas and nodular fibrohyaline scars were observed in three other cases of the disorder (Pimental and Menezes, 1975). Estimates of the level of exposure were not reported in any of these studies. It should be noted, however, that the adverse conditions found in vineyard workers may be complicated by concomitant exposures to many other agents in addition to Bordeaux mixture. For instance, vintners have been reported to experience elevated exposures to arsenic compounds used in vineyards (USEPA, 1980a) and arsenic inhalation exposures have been implicated as possible causative agents for lung cancers.

In another study examining cytologic changes of the respiratory tract in vineyard sprayer workers, professional inhalation of copper sulfate was shown to affect the respiratory epithelium and the pulmonary parenchymal (Plamenac et al., 1985). Sputum specimens from 52 rural workers engaged in vine-spraying Bordeaux mixtures (1.5% copper sulfate solution) were compared with 51 rural workers from the same region who did not work in the vineyards and did not come in contact with the copper sulfate solution. Subjects were 25-55 years of age with normal chest roentgenograms and were subdivided into smokers and nonsmokers. The vineyard workers averaged 9 years of exposure. Results showed enhanced expectoration of sputum in a high percentage of vineyard sprayers and considerably more frequent than those of the control group. Atypical squamous metaplasia was noted in 29% of smoking vineyard sprayers. The authors (Plamenac et al., 1985) suggest that occupational exposure to the copper (i.e., the copper sulfate solution) may be a significant etiological factor in the occurrence of bronchogenic carcinoma in these individuals. The presence of large numbers of eosinophils in the sputa of vineyard sprayers suggests the possibility of an allergic reaction to the Bordeaux mixture (i.e., to one of its constituents). However, the investigators concluded that it is uncertain which mechanism (toxic, allergic or inflammatory) was responsible for the occurrence of changes in the respiratory epithelium (Plamenac et al., 1985).

Most reports of copper intoxication have resulted from ingestion of copper compounds usually by accidental poisonings, suicide attempts or drinking copper-contaminated water. Typical symptoms include GI irritation, headache, dizziness and a metallic taste in the mouth. Table 13 summarizes the health effects of ingested copper in humans.

Chuttani et al. (1965) reported the clinical data from 53 cases of acute copper sulfate poisonings. Ingestion of up to 12g copper resulted in immediate metallic taste, nausea, vomiting, epigastric pain, diarrhea, jaundice, hemoglobinuria and/or hematuria, anuria, oliguria, hypotension and coma. Autopsy of five patients revealed ulceration of the gastric mucosa, hepatic centrilobular necroses, biliary stasis and renal tubular cell necrosis.

Daily intakes of copper ranging from 2-32 mg due to contaminated drinking water has reportedly caused general gastric irritation characterized by nausea, vomiting, abdominal cramps and diarrhea (see Table 13) (Spitalny et al., 1984; Nicholas and Brist, 1968; Semple et al., 1960; Wyllie, 1957).

Copper sulfate has been involved in a number of poisoning episodes that involved doses of copper ranging from <1-20 g. An 18-month-old boy who drank a solution containing 3 g cupric sulfate (~1.2 g Cu) developed acute hemolytic anemia, reduced glucose-6-phosphate dehydrogenase activity, hematuria, glycosuria and proteinuria. High copper levels in serum and urine were also observed (Walsh et al., 1977). The child gradually recovered and after 1 year clinical signs were normal with serum copper levels within the normal range. A 24-year-old man ingested ~600g of copper sulfate over a 4-month period (~2 g Cu/day) and developed symptoms that included gastrointestinal pain and hemolytic anemia (Roberts, 1956). The patient was discharged after 2 weeks with only mild signs of anemia. No follow-up examination was conducted.

A 27-year-old man who ingested at least 50 g of copper sulfate (20 g Cu) was reported by Chugh et al. (1975) to be cyanotic, oliguric and anemic. The patient also showed signs of severe intravascular hemolysis and methemoglobinemia and died 16 hours after the poisoning. Another episode of copper sulfate poisoning (the amounts were unknown) resulted in sulfhemoglobinemia, acute tubular necrosis, renal failure and death (Sanghvi et al., 1957). In this case, however, anoxia caused by sulfhemoglobinemia may have caused the renal necrosis (USEPA, 1985) implying that sulfate

Table 13. Effects of Oral Exposure of Copper and Copper Compounds in Humans

Sex/Age/ Number	Compound	Vehicle	Exposure	Dose (mg Cu/kg/ day)	Effect	Reference
Male/32/1	copper	drinking water	2-8 mg/l for 1.5 years	0.06-0.23[a,b]	Episodic emesis and abdominal pain	Spitalny et al., 1984
Female/5,7/2	copper	drinking water	2-8 mg/l for 1.5 years	0.1-0.4[c]	Episodic emesis and abdominal pain	Spitalny et al., 1984
Male, female/ 14-60/53	copper sulfate	oral ingestion	1-30 g $CuSO_4$	6-171[b] 7-210[d]	Diarrhea, hemoglobinuria, and/or hematuria, anuria, jaundice, oliguria, death, coma, hypotension[e]	Chuttani et al., 1965
Male/NR/20	copper	contaminated tea	8 oz. tea containing ≥30 ppm Cu	≥0.1[b]	Diarrhea, nausea, vomiting[d]	Nicholas and Brist, 1968
Male/NR/150	copper sulfate	contaminated tea	8 oz. tea containing ≥44 ppm Cu	≥0.14[b]	Gastroenteritis, dizziness, headache in 18/150	Semple et al., 1960
Female/NR/15	copper	contaminated cocktails	5-32 mg estimated exposure from cocktail shaker	0.09-0.55[d]	Weakness, abdominal cramps, headaches, nausea, dizziness and vomiting in 10/15	Wyllie, 1957
Male/2/1	copper sulfate	oral ingestion	3 g (1 dose)	120[f]	Hemolytic anemia, hematuria, glycosuria, poteinuria	Walsh et al., 1977

Table 13. **(continued)**

Sex/Age/ Number	Compound	Vehicle	Exposure	Dose (mg Cu/kg/ day)	Effect	Reference
Male/27/1	copper sulfate	oral ingestion	50 g (1 dose)	286[b]	Cyanosis, oliguria, severe intra-vascular hemolysis, methemoglobinemia; death within 16 hours	Chugh et al., 1975
Male/24/1	copper sulfate	water	600 g over a 4-month period	29[b]	Gastrointestinal pain, hemolytic anemia	Roberts, 1956

[a]Assumes an adult daily water intake of 2 l
[b]Assumes adult 70 kg man
[c]Assumes a weight of 20 kg and a daily water intake of 1 l for a child
[d]Assumes adult 58 kg women
[e]Listed in order of frequency
[f]Assumes 10 kg child
NR = Not reported

may have contributed to the effects of the poisoning. Stein et al. (1976) reported the death of a 44-year-old female after being given an emetic dose of copper sulfate (796 mg Cu) administered after the patient had ingested alcohol and diazepam. The woman suffered from respiratory collapse, massive gastrointestinal hemorrhage, hemolytic anemia and renal and hepatic failure. Autopsy revealed acute renal tubular necrosis and a liver copper concentration of 75 ppm. Copper was responsible for most of these effects as they are consistent with those seen in other copper sulfate poisoning incidents.

Children may be especially susceptible to copper overdoses. A 15-month-old boy developed symptoms that included prostration, vomiting, red extremities, hypotonia, photophobia and peripheral edema (Salmon and Wright, 1971). The serum copper level was very high (286 μg/100 ml) while the plasma ceruloplasmin level was essentially normal (22.5 mg/100 ml), thus eliminating the possible involvement of Wilson's disease. These effects were presumably caused by the copper content (0.35-0.79 mg/l) in the drinking water ingested over a 3-month period, suggesting that some infants may be responsive to daily intakes of <1 mg copper/day.

A disease known as Indian Childhood Cirrhosis has frequently been associated with high intakes of copper in children ranging in age from 6 months to 5 years (Bhandari and Sharda, 1982; Bhargava, 1982; Chaudhary, 1983; Pandit, 1982; Pandit and Bhave, 1983; Sharda, 1984; Tanner et al., 1983). This disorder is characterized by widespread hepatic necrosis, Mallory's hyaline inclusions in many hepatocytes, intralobular fibrosis, poor regeneration and very high hepatic copper content (Pandit, 1982; Pandit and Bhave, 1983). It is generally believed that milk and water stored in brass and copper containers leads to increased dietary copper in children, which is at least partly responsible for the pathogenesis of the disease (Bhandari and Sharda, 1982; Bhargava, 1982; Sharda, 1984). In addition, many of the epidemiological features of Indian Childhood Cirrhosis (sibling studies, geographical and religious influences) can be explained by this hypothesis (Chaudhary, 1983; Tanner et al., 1983).

Other epidemiology studies have failed to establish a definite link between chronic exposure to copper and cancer or other diseases. Increased mortality from hypertension or hypertensive heart disease and elevated rates of cancer of the trachea, lung, bronchus, liver and biliary passages have been observed in counties containing primary copper smelters (PEDCo, 1978); however, copper ore concentrates also contained arsenic, lead, nickel, antimony and selenium and the authors cautioned against overemphasizing the association between copper and increased disease rates.

Schrauzer et al. (1977) reported that there is a direct proportionality between blood copper concentrations and mortality due to cancer of the intestine in males and females and cancer of the lung, breast and thyroid in females. The authors contended that excess copper in the diet may be the cause of the elevated blood copper levels. Morton et al. (1976) observed a significant negative association between copper concentrations in tap water samples and central nervous system malformations (e.g., anencephalus, neural tube malformations) in South Wales. These associations, however, can only be critically evaluated when additional epidemiological information becomes available.

9.2. Populations at Risk

Several populations may be considered especially susceptible to excess environmental copper exposure. The following sections discuss these groups briefly.

9.2.1. Wilson's Disease—Hepatolenticular degeneration, also known as Wilson's disease, is an autosomal recessive disorder (Scheinberg, 1979) that occurs in perhaps 1 of 200,000 individuals (Schernberg and Sternlieb, 1969). This disease affects normal copper homeostasis and is characterized by an excess retention of hepatic copper, decreased concentration of plasma ceruloplasmin, impaired biliary copper excretion and hypercupuria (Evans, 1979; Schroeder et al., 1966). Increased copper deposition in the brain, kidneys and cornea are also characteristic of Wilson's disease (see Table 6) (Evans, 1973). Limiting copper intake through air, water and food is essential in treating the disease (Schroeder et al., 1966). It is apparent that patients with this disease should have low intakes of copper. This has been mainly achieved in the past by checking and limiting copper intake from water and diet. When air concentrations are low, the contribution of copper from air to the total absorbed amount of copper will still be negligible, since this air amount will be far below the concentrations from food and water.

9.2.2. G6PD Deficient Individuals—An inherited deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) was first discovered in 1956, and was found to be the basic defect in cases of hemolytic anemia following exposure to certain drugs, mothballs and fava beans (Naiman and Kosoy, 1964). This abnormal gene has been shown to be more prevalent in newborns of Chinese, Greek and Italian origin (Naiman and Kosoy, 1964). It has been estimated that 13% of the male American black population has a hereditary deficiency of red blood cell G6PD, an enzyme whose activity is also known to be reduced in Wilson's disease patients (Diess et al., 1970), in acute copper sulfate poisoning cases (Chugh et al., 1975) and in human erythrocytes incubated with 0.1 mM copper (Bouland et al., 1975). This enzyme is essential to the formation of NADPH which is necessary to produce reduced glutathione (GSH), the major intracellular thiol active in protecting against free radicals and oxidizing agents. Individuals with this enzyme deficiency may be at increased risk to the hematologic effects of copper caused by a reduction in the amount of red blood cell GSH (Calabrese et al., 1979, 1980; Calabrese and Moore, 1979). However, Goldstein et al. (1985) reviewed the available exposure and hematological data pertinent to G6PD deficient individuals and concluded that a significant reduction in GSH would most probably not occur and even if it did, serious consequences such as chronic anemia would be highly unlikely. The authors further stated that even if a decrease in red cell GSH led to a fall in hematocrit (a "worst case" scenario), functional deficits would be highly improbable. Finally, it was concluded that "exclusion from the workplace on the basis of susceptibility to oxidant hemolysis of the more than 1,000,000 black Americans with this genetic variation is inappropriate." In humans with a preexisting condition (e.g., G6PD-deficient individuals) the threshold for copper exposure may be expected to be lower than those in the population without the condition. There is considerable controversy as to whether these individuals represent a population at risk to excess copper exposure in the workplace or general environment.

9.2.3. Hemolysis Patients—Several kidney dialysis patients exposed to excess copper in the dialysate have reportedly suffered from acute hemolytic anemia and may also be considered a population at risk (Williams, 1982). Hemolysis in copper poisoning is caused mainly by a large exposure to copper, resulting in free copper ions in the blood (e.g., during dialysis). The homeostatic mechanisms will prevent the accumulation of free copper ions, even during high-industrial exposure. This problem, however, can be controlled by closely monitoring the pH and conductivity of the dialysis fluid

(Williams, 1982), and exposure to airborne copper would not be expected to exacerbate this condition.

9.2.4. Infants and Children—Infants and children are also susceptible to the effects of copper as evidenced by the incidence of Indian Childhood Cirrhosis and the reports of copper intoxication in young children caused by drinking water containing moderate levels of copper. Because the fetus and newborn have elevated hepatic copper levels (Sternlieb, 1980) and since homeostatic mechanisms are not fully developed at birth (Underwood, 1977), the newborn represents a risk group that may not be able to cope with excess copper exposure. The fetus does not have an "abnormal burden" of copper; it needs a store of copper from which it will start using as a newborn.

As a specific diet-linked syndrome, Indian Childhood Cirrhosis is apparently not a health problem in the United States because of better cooking methods. However, in small children, ingestion of ~1 mg Cu/kg bw or 10 mg Cu/10 kg child/day from contaminated milk can cause severe liver disorders (Tanner et al., 1983). These data are relevant in the United States mainly in defining a dose-response relationship in very young children regardless of the source of exposure. Given that 1 mg/kg bw is an upper limit of exposure, it is conceivable that, for instance, 20% of this level (2 mg/child/day) could result in less severe, though still significant, liver damage. This intake is well within the normal adult recommended nutritional level, indicating that children may be more susceptible systemically to copper than adults. The main action may be the intestinal mucosa, especially in infants with pre-existing GI tract disturbances. Thus, preparation of the formula with tap water with high copper concentrations may create some health problems. There is very little possibility that the small amounts in ambient air can play a role in this association.

Indian Childhood Cirrhosis data are also relevant to infants and toddlers living around copper smelters where mouthing activities can put them at high risk. Children living near these smelters where copper concentrations in soil can exceed 50,000 ppm (Nriagu, 1979) may ingest >5 mg Cu/day which is well above the level at which signs of copper toxicosis in children appear. This figure is based on the observation that children ingest an average of 100 mg soil/day (USEPA, 1980c). It is, therefore, important to recognize that children and infants appear to be more sensitive to copper intake and extra care should be taken to prevent excess exposure through food, water, air and soil especially in hot spot areas.

The fetus (i.e., occupationally-exposed working mother) may also represent a population at risk since fetal copper distribution is markedly different from that in the adult (USEPA, 1980b). Also, there is no apparent trans-placental barrier to fetal copper uptake and homeostatic mechanisms (ceruloplasmin synthesis) are not completely expressed *in utero*. Thus, the fetus can act as a copper depot, making it extremely sensitive to increases in maternal exposure and indicating that there is a potentially large population at risk. Again, pregnancy is a normal physiological state with its own set of values. In pregnancy, it is recommended to increase the intake of essential elements. The fetus has high levels, but these levels will drop as the newborn starts using the copper after birth.

9.2.5. Combined Exposure Populations—These probable populations at risk (previous four groups) are diversely scattered throughout the United States. The highest individuals at risk when exposed to copper would be those persons who belong to more than one group.

Marecek and Nevstmalova (1984) reported on a study of heterozygous children and adults whose parents were diagnosed with Wilson's disease. These investigators observed the serum copper and ceruloplasmin levels and rates of urine copper excretion before and after exposure to penicillamine. Wilson's heterozygotes are difficult to distinguish from asymptomatic patients, particularly in siblings. The siblings showed decreased levels of both serum copper and ceruloplasmin. Serum ceruloplasmin and copper levels in the 16 children studied were significantly reduced as compared with those of 20 healthy children of the same age. The differences were pronounced if compared with a heterozygous adult population, where reduced ceruloplasmin values were found in only 18% (Marecek and Nevstmalova, 1984). The authors found that it is quite conceivable that in children with a partial defect of ceruloplasmin synthesis, the level of synthesis will lag behind that found in the normal population, reaching the normal physiological values later in life. These authors indicated that only a long-term follow-up can show whether these are merely temporary phenomena or whether they will persist until adulthood. This position is contrary to Sternleib's viewpoint, in which he stated that heterozygous carriers never become clinically ill and need no treatment (Sternlieb et al., 1973). More definitive research must be undertaken before this group can be identified as one at risk to high copper levels.

10. Assessment

10.1. Overview

Although there is substantial published literature on copper and copper-related compounds, supporting information for determining the noncancer health effects from exposure to copper by inhalation is very limited. Copper is an essential element with ~2-3 mg/day being required for proper nutrition. However, excessive human exposure to copper has been shown to create acute toxic effects. In the human body, there are demonstrated homeostatic mechanisms which control copper levels and regulate tissue levels so as not to bioaccumulate copper in large amounts and to distribute it to all human tissues. However, in cases of excess copper absorption or abnormal metabolism, such as Wilson's disease, the metal can accumulate and exert detrimental and toxic effects.

Although its production volume has decreased in recent years, copper is still produced in high volume, with its atmospheric anthropogenic flux being 3 times higher than that from natural sources. In the urban sector, major sources of copper to the atmosphere are from incineration and automobile exhaust, while in the highest (hot) spots of copper levels in air, the sources are ore processing and smelting. Human exposure to copper in air in the United States can vary widely depending on the locality and copper-related industries in the area.

The average MMD of copper aerosol is ~1.3 μM. Since particulate matter in the size range of 0.5 and 5.0 μM is commonly assumed to be respirable, most available copper in the atmosphere is respirable. Again, this is dependent upon locale since the particle size is source dependent. However, inhalation of air containing background levels of copper would contribute negligible amounts (<1%) to the average daily intake of copper. Direct inhalation of copper by humans at the reported levels in this document have been shown to add much less to body burden than exposure through ingestion and drinking water. With these intake levels, one estimate has shown that the inhalation pathway contributes no more than 0.15 μg/kg to a total copper body burden of ~800 μg/kg.

Given this brief analysis, there still remains several identifiable populations (subgroups) at risk to high levels of copper. These include infants and young children and the developing fetus, as well as individuals with Wilson's disease. These groups are susceptible to excess copper exposure either because of an inborn error in copper metabolism or because of underdeveloped homeostatic mechanisms combined with higher relative copper body burdens. In addition, members of these groups that are located in hot spot areas and occupational settings should be considered more susceptible because of their inability to deal with the higher ambient levels of copper and combined exposures. Multimedia exposures to copper, combined with deficiencies or excesses of other compounds that interact with copper in the body, may cause adverse human or animal health effects. Interactive relationships between copper and elements such as cadmium, zinc, iron and molybdenum are germane to the assessment of copper's health effects, since the degree of both exposure (i.e., the amount absorbed) and the expression of systemic effects are modulated by these elements. These interactions have been reviewed in the literature for copper, but the degree to which these

interactions are expressed during the inhalation process has not been well documented.

10.2. Principal Effects and Target Organs

The effects of airborne copper fumes, dusts or mists result primarily from industrial exposures and are manifested predominantly by dermatologic and respiratory symptoms. As shown in Chapter 9, cases of copper intoxication are rare, with the exception of metal fume fever seen in occupationally-exposed individuals. In general, acute effects of copper intoxication are readily reversible after removal of the offending agent. In the vineyard workers, the combined exposure to copper and other agents has been related to lung cancer. Chronic inhalation data on copper is very limited because exposure is found in the presence of the other offending agents. Mild anemia, contact dermatitis and leukocytosis have been observed in long-term occupational exposures to copper.

Copper is distributed to all body parts, with the liver being the main storage depot for copper. The specific etiology of copper-induced liver damage has not been completely determined. Kidney damage has been associated with copper toxicosis. In laboratory rats, excess copper ingestion caused renal tubular damage and renal failure. In suicide victims using copper sulfate, hematuria, hemoglobinuria and oliguria were found. One hypothesis for the observed renal effects was that copper thioneine leaked from the liver of copper-poisoned animals and was responsible for the subsequent renal damage. In the sheep studies, the investigators described sudden hemolytic crises in copper-poisoned animals.

Wilson's disease individuals and patients undergoing kidney dialysis using copper components have suffered hemolytic anemia. In the lungs, adverse effects such as metal fume fever and vineyard sprayers' lung are associated with copper inhalation. Other body parts have been shown to be affected by excessive copper exposure.

10.3. Factors Influencing Health Hazard Assessment from Inhalation of Copper

In reviewing the various factors determining the health effects from inhalation of copper, it is apparent that increases from ambient air exposure add little to the copper body burden for normal individuals. However, the data base for determining these effects from copper, *per se*, is very weak. In almost every case presented in this document, the exposure is to a copper-related compound or combined with other compounds, making an individual chemical assessment difficult. In the exposure area it has been shown that the population at large is exposed to copper through a variety of media and that copper intake is essential to nutritional health. There is no available evidence that human health effects have resulted from nonoccupational inhalation of existing ambient air levels. Direct exposure through inhalation of copper by humans at the reported levels in urban and rural areas of the United States contributes significantly less to the body burden than ingestion does, and does not appear to be a health issue to those individuals able to handle excess levels. However, different biological or homeostatic mechanisms may account for different pharmacokinetics and elicitations of any toxic effect. This may not necessarily be true for those individuals in the susceptible populations which are identifiable and shown in Chapter 9.

In the only chronic inhalation study reviewed in Chapter 8, Pimental and Marques (1969) exposed a group of 12 guinea pigs to an atmosphere saturated with Bordeaux mixture for over 6 months. However, this study cannot be

used for determining any quantitative risk assessment because 1) the study size and experimental techniques are limited; 2) the exposure was to Bordeaux mixture, an aqueous solution of lime and copper sulfate and some effects may be from lime not copper; and most importantly, 3) a daily copper exposure level cannot be derived from this study.

There is no available evidence to show that copper exposure, *per se*, is carcinogenic. Studies concerning the carcinogenicity, mutagenicity and teratogenicity of inhaled copper or copper compounds could not be located in the available literature. However, some short-term tests have indicated that certain of the copper salts may have characteristics suggestive of carcinogens. The overall weight-of-evidence suggests that there are insufficient data to determine the carcinogenic potential of copper to humans. Therefore, based on the USEPA's Guidelines for Carcinogenic Risk Assessment (USEPA, 1986), copper is classified in Group D: Not classifiable. Limited epidemiological data have failed to establish a link between copper exposure and cancer or other disorders. Industrial copper inhalation exposures have elicited mild, infrequent and transient effects, with airborne copper being less bioavailable than copper from food and water.

The special subgroups are identifiable and in most cases personal protective measures can be taken to prevent excess copper exposure. A controversy still remains as to whether the American black population with the hereditary G6PD red blood cell deficiency represents a population at risk. These populations are scattered throughout the United States; however, those individuals with the highest possibility of excess exposure would be found in areas known as hot spots or ore processing and smelting areas.

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